



Press release
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Malaria – “Wake and kill:” a new concept for the elimination of relapse

A team of researchers coordinated by Prof Dominique Mazier (AP-HP, UPMC, Inserm Unit 1135, CNRS ERL 8255) and Dr Georges Snounou, Research Director at CNRS (UPMC, Inserm Unit 1135, CNRS ERL 8255) has succeeded in culturing the dormant hepatic stage of the malaria parasite, previously inaccessible to researchers. The initial results from this technical breakthrough have enabled the development of a new concept for the elimination of malaria relapse due to the activation of these dormant forms. It should enable the establishment of a new strategy for the management of this illness, which would involve combining a drug capable of activating the dormant parasite with one of the many drugs effective against the parasite.

These results have just been published in the journal *Nature Medicine*.*

Present-day management of malaria

After the bite from an infected mosquito, the parasite that causes malaria reaches the liver, where it multiplies. It then propagates in the bloodstream, where its proliferation causes a potentially fatal illness. In some cases, including that of the parasite *Plasmodium vivax* in humans, a fraction of hepatic parasites may remain “dormant” for a year or more, hence their name, **hypnozoites**. These subsequently “wake,” or reactivate, over time, and give rise to a bloodstream infection. This feature is probably the source of the belief that malaria persists for life.

The hypnozoite constitutes a two-fold problem in terms of controlling/eliminating malaria—a greater number of cases needing treatment, and increased transmission. Unfortunately, primaquine, and a recently developed analogue, tafenoquine, the only drugs capable of killing hypnozoites, have adverse effects on the body that are sometimes serious. The identification of reliable alternative drugs therefore constitutes a public health emergency. Until now, the search for new anti-hypnozoite drugs has been based on observations made in humans infected with *P. vivax*, or in monkeys infected with a parasite related to *P. vivax*, *Plasmodium cynomolgi*.

Methodology

Through a collaboration with teams from the national IDMIT Center¹ at the French Atomic Energy and Alternative Energies Commission (CEA), and those of the **Biomedical Primate Research Centre (BPRC)** in the Netherlands, the team led by Prof Dominique Mazier and Dr Georges Snounou first succeeded in maintaining cultures of infected hepatic cells for 40 days, i.e. nearly four times longer than is usually achieved. The team then demonstrated the persistence of dormant stages throughout the duration of culture, with some reactivating over the time, thus mimicking what happens in humans. It also tested new drugs (discovered at the Institut Pasteur in Paris), which inhibit epigenetic factors, on these hypnozoites. These drugs act by targeting histone methyltransferases, and are able to kill the blood stage of the parasite. Paradoxically, one of them activated the hypnozoites. **This unexpected result led the team to formulate a new strategy, “Wake and Kill,” which involves combining a drug that activates the dormant parasite with one of the many available treatments known to be effective against the multiplying parasite.**

Results provide hope for the management of malaria

Thanks to this methodology, developed via an international and multi-institute collaboration (Inserm, CNRS, CIMI, CEA, UPMC, AP-HP, Institut Pasteur Paris), it will now be possible to screen drugs *in vitro* for their anti-hypnozoite effect, thus limiting the need for animals. The challenge is to adapt this technique to screening a large number of compounds. In addition, the possibility of growing hypnozoites in culture will finally allow scientists to study this enigmatic parasite stage, described 100 years after the discovery of the causative agent of malaria by Laveran in 1880.

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¹ Infectious Diseases Models For Innovative Therapies

Persistence and activation of malaria hypnozoites in long-term primary hepatocyte cultures

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