A new breakthrough in developing effective antimalarial drugs

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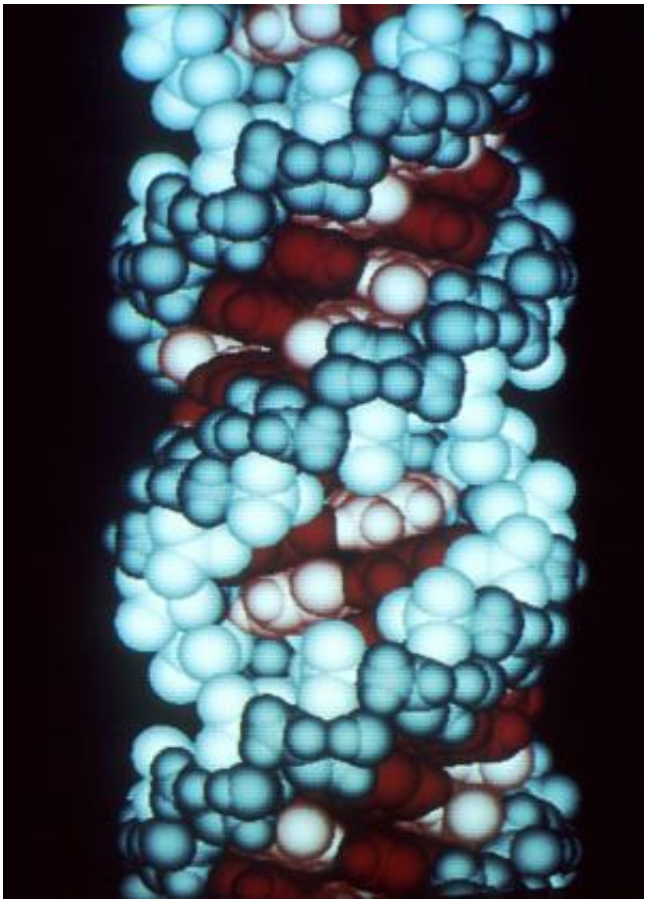

This is a computer graphic of an RNA molecule. Credit: Richard Feldmann/Wikipedia

Parasites in the genus Plasmodium, which cause malaria, are transmitted to humans through bites from infected mosquitoes. The parasites

acclimatize to these two completely different hosts because the plasticity of their genome enables them to adapt as necessary. Scientists at the Institut Pasteur and the CNRS have investigated the epigenetic mechanisms behind this plasticity, in particular, DNA methylation. They identified molecules capable of inhibiting DNA methylation and effectively killing even the most resistant Plasmodium falciparum parasites. The results of their research were published on November 27, 2019 in the journal *ACS Central Science*.

Malaria affects more than 200 million people worldwide every year, and resistance to antimalarial treatments is constantly increasing. This infectious disease is caused by Plasmodium parasites that are capable of adapting to varied environments. During the parasite's life cycle, it lives in the salivary glands of the mosquito vector before infecting the liver and then the blood of the human host. "At each stage in the cycle, epigenetic mechanisms such as histone or DNA modifications regulate the expression of the parasite's genes, enabling the specific expression of some genes in the cell at a given time so that the parasite can adapt to its environment," explains Flore Nardella, a contract researcher in the Biology of Host-Parasite Interactions laboratory (Institut Pasteur/CNRS/Inserm).

In 2019, her laboratory, led by CNRS scientist Artur Scherf, demonstrated the importance of epigenetic DNA modifications for the parasite's life cycle. The Institut Pasteur's Epigenetic Chemical Biology laboratory has unparalleled expertise in the field of DNA methyltransferase inhibitors. So it was logical for the two teams to work together to identify molecules capable of inhibiting DNA methylation and killing parasites. "Artur's team had a thorough knowledge of the epigenetic mechanisms in malaria, and we had an original chemical library with inhibitors that had already been optimized for these modifications," explains Paola B. Arimondo, a chemist, CNRS Director of Research and Head of the Epigenetic Chemical Biology Unit (Institut

Pasteur/CNRS).

So the scientists decided to work on the Plasmodium falciparum parasite, especially strains of artemisinin -resistant parasites provided by the Institut Pasteur du Cambodge. In a first series of in vitro experiments, the Plasmodium falciparum parasites were allowed to interact with human red blood cells so that they could infect and develop in them. More than 70 methylation-inhibiting molecules were then tested to assess their efficacy and their specificity in relation with the parasites.

"As soon as we tested the first molecules, we saw significant activity, comparable with drugs such as chloroquine," says Flore Nardella. "That's very rare when testing a new library of molecules." "The inhibitor molecules were very effective, and some of them killed the Plasmodium falciparum parasites in the blood in just six hours," says Paola B. Arimondo.

The scientists then continued their research. In a second series of experiments, the most effective molecules were tested on resistant isolates and, once again, the results were conclusive: the molecules effectively killed the blood parasites. "This study shows, for the first time, that parasites in the blood, including artemisinin-resistant strains, can be killed rapidly by targeting DNA methylation," concludes Paola B. Arimondo. "Given the treatment failure observed in South-East Asia in particular, it is important to find new therapeutic targets. Methylation could pave the way for new drugs that, combined with artemisinin, could eliminate resistant parasites," adds Flore Nardella.

For the third stage of their work, the scientific team tested the inhibitors in vivo in mice infected with the parasite Plasmodium berghei. Once again, the approach proved successful: the treatment killed the blood parasites and the mice survived the cerebral malaria infection. The next steps for the two research teams are to continue optimizing the

selectivity and efficacy of the most promising molecules (this is crucial if the molecules are to be used in humans) and to identify molecules that may act on other development stages of the parasites responsible for transmission.

More information: Flore Nardella et al, DNA Methylation Bisubstrate Inhibitors Are Fast-Acting Drugs Active against Artemisinin-Resistant Plasmodium falciparum Parasites, *ACS Central Science* (2019). DOI: 10.1021/acscentsci.9b00874

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