Hope for effective new malaria treatment

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A research project carried out jointly by chemists at Imperial College London in the United Kingdom and biological scientists at the Institut Pasteur/Centre National de la Recherche Scientifique (CNRS) in France have opened the door to a promising new treatment for malaria. The researchers have successfully identified a new means to eradicate blood-borne Plasmodium parasites that cause the disease. Their research was supported in part by a European Research Council (ERC) grant.

Malaria causes up to 3 million deaths each year, particularly afflicting vulnerable people such as children under the age of five, and pregnant women. It is predominantly prevalent in tropical regions of Africa, Asia, and Latin America. In addition, 102 cases were reported in Europe by the World Health Organization (WHO) in 2011. Although treatments for malaria are currently available, the Plasmodium parasite is rapidly becoming resistant to the most common drugs, and new strategies to tackle the disease are desperately needed.

The collaborating research groups have identified a potential new malaria drug consisting of molecules that interfere with parasite histone methyltransferases, enzymes crucial to the parasite's growth and viability during the blood stage of its lifecycle. The new drugs rapidly kill parasites in culture, and are also able to greatly reduce parasite infection in mice in a single day. These results were published in the *Proceedings of the National Academy of Sciences* (*PNAS*) in October.

Dr Matthew Fuchter from Imperial College London spoke about the importance of finding new treatments, and the new weakness in the parasite that both teams discovered: 'Plasmodium falciparum causes 90 per cent of malaria deaths, and its ability to resist current therapies is spreading dramatically. Whilst many new drugs are in development, a significant proportion are minor alterations, working in the same way as current ones, and therefore may only be effective in the short term. We believe we may have identified the parasite's "Achilles' Heel", using a molecule that disrupts many vital processes for its survival and development.'

The research teams have successfully identified two chemical compounds that affect *Plasmodium falciparum's* ability to carry out transcription, the key process that translates genetic code into proteins. Unlike the majority of antimalarial drugs, these compounds are able to kill the parasite during the 48-hour blood borne period of its complex

life cycle, when it is growing and differentiating.
'One particularly exciting aspect of this discovery is this new molecule's ability to rapidly kill off all traces of the parasite, acting at least as fast as the best currently available antimalarial drug,' noted the principle investigators of this study.

Initial tests in the Arthur Scherf laboratory at the Institut Pasteur also showed the molecules were able to kill strains of Plasmodium that have developed a resistance to current treatments, although the scientists say more experiments are needed to confirm these results. The group hopes to refine these molecules, which would improve their effectiveness, and it aims for this to be a viable strategy for treating malaria in humans. The scientists hope it will lead to the development of an effective malaria cure within the next 10 years.

More information: Malmquist, N. A. et al., 'Small-molecule histone methyltransferase inhibitors display rapid antimalarial activity against all blood stage forms in Plasmodium falciparum', *PNAS*, 109(41): 16708, 2012. doi:10.1073/pnas.1205414109

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