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Nijmegen-led collaboration generates innovative candidate drug against malaria

A molecule once designed to cure the skin disease psoriasis appears to be particularly effective against malaria. The antimalarial properties were revealed thanks to one researcher's inspired hunch when the psoriasis drug discovery programme came to a dead end. The candidate drug offers considerable potential for combating this infectious disease.

The research that led to this candidate has been published in Science Translational Medicine.

The new candidate, a pantothenamide molecule, closely resembles a molecule that occurs naturally in malaria parasites. Therefore, the parasite uses pantothenamide in much the same way in its metabolism, except that it interferes with the metabolism of the single-celled malaria parasite, which then dies.

Laboratory models of malaria suggest that the administration of a single dose of the candidate drug may cure the disease completely, making it attractive in comparison to existing 3-day treatments. Additionally, it is cheap to manufacture – a critical factor in the development of a new antimalarial medicine – and it also stops the transmission of the malaria parasite from humans to mosquitoes. This means that if it develops into a full-fledged medicine, it may also help to eradicate malaria. Research leader Koen Dechering from TropIQ Health Sciences in Nijmegen highlights that: 'The molecule has a mechanism of action that hasn't been used before. This means that there's no resistance to the drug yet and it is possibly effective against all forms of malaria. Because parasite resistance to malaria drugs has historically been a major problem and remains a concern, we are hopeful that we are very close to a breakthrough.'

From psoriasis to malaria

The research that led to this candidate drug has an extraordinary history. Biologist Joost Schalkwijk from the Dermatology Research Laboratory at the Radboud university medical center was initially trying to cure psoriasis, a skin disease. But the molecules that he created, together with the Department of Synthetic Organic Chemistry at Radboud University and spin-off company Chiralix, proved unusable for that disease.

In a book dating back to 1946, however, Schalkwijk found that related compounds could cure malaria in chickens. Schalkwijk: 'That was when I began testing the molecules as a way of combating malaria, together with Robert Sauerwein from the Department of Medical Microbiology at the Radboud university medical center. They did indeed prove lethal for the single-cell *Plasmodium* parasites that cause malaria in humans.' The research then focused on finding a form of the molecule that is safe, potent and can be

produced quickly. The first pantothenamide compound coming out of this research is now ready for clinical development to determine safety and effective dosages.

An international consortium

Soon after the discovery of the first substances some 10 years ago, a partnership developed between Radboud university medical center and the Nijmegen-based spin-off TropIQ Health Sciences, with financial and scientific support from the not-for-profit product development partnership (PDP), Medicines for Malaria Ventures (MMV), the Dutch Government's PDP III Fund, and partnership management support from Lygature, Utrecht. This partnership resulted in a research team comprising spin-offs TropIQ and Chiralix, the Dermatology and Medical Microbiology departments at Radboud university medical center, the Synthetic Organic Chemistry department at Radboud University, Hermkens Pharma Consultancy and a number of international partners, including the laboratory of Manuel Llinás at Pennsylvania State University in the United States. MMV is now responsible for taking the compound through the next stages of development with pre-clinical studies in the laboratory to determine safety, followed by first-in-human clinical studies.

About malaria

With around 216 million cases and 400,000 deaths a year, malaria is one of the most deadly infectious diseases of our time. Recent years have seen a rise in the number of people infected, particularly in sub-Saharan Africa and South America.

The deadliest form of malaria is caused by a single-celled parasite, *Plasmodium falciparum*, which is transmitted by mosquitoes. Once transmitted, the parasite develops in five phases from an asexual cell to mature male and female cells. These cells can then be ingested again by mosquitoes, after which the parasites are fertilized in the mosquitoes' stomachs. The offspring can return to humans following a mosquito bite. Preventing the transmission of malaria is viewed as one of the greatest challenges in the fight against this disease.

Antimalarial pantothenamide metabolites target acetyl–coenzyme A biosynthesis in Plasmodium falciparum. Science Translational Medicine Vol. 11, Issue 510, eaas9917

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