In their quest to find new chemical entities for malaria drug development, Amanda Rousseau, CSIR principal researcher, and her fellow chemists David Gravestock, Arina Lourens and Simon Maleele, are concentrating on antifolates, a class of drugs that targets folate metabolism in *Plasmodium falciparum*, the parasite that causes malaria.

Their discovery of a series of compounds that has shown remarkably potent activity against a resistant strain of *Plasmodium falciparum* could potentially lead to a drug candidate. Their discovery has generated interest from investors and a full proposal for an interested party is under development.

Explaining the mode of action of antifolates in general, Rousseau says that folic acid derivatives are essential components in a number of key cellular processes in living organisms, for example DNA synthesis. Humans get their supply of folic acid from their diet, as the human body can’t make it, although the body does have the ability to recycle the ingested supply. The parasite on the other hand, has the ability to both synthesise and recycle folic acid derivatives. “Antifolates are drugs that inhibit the ability of the parasite to make and recycle folic acid,” she says.

“Drugs targeting only the de novo synthetic pathway in the parasite – responsible for the synthesis of folate derivatives – are generally not all that effective when administered on their own and combination therapies are often used. The particular class of compounds we have designed targets the salvage pathway in the parasite, which is responsible for recycling folate derivatives.”

She adds that when designing a drug that targets this pathway, the subtle differences in enzyme structure between the parasite and man must be taken into consideration, to ensure that man’s ability to recycle folic acid is not inhibited.

Rousseau says the team chose to work on antifolates because this class of drugs is cheap to produce – an important consideration in the African context. To boot, the target – the enzyme dihydrofolate reductase-thymidylate synthase (DHFR-TS) – is well known, and the mechanisms of drug resistance are very well understood.

While the essence of the innovation will be kept confidential until patents have been granted, Rousseau reveals that the innovation centres on the ability of their series of compounds to be sufficiently flexible to inhibit both drug-sensitive and drug-resistant forms of the parasite.

But Rousseau points out that finding a new active compound is only the beginning. “Finding an active compound does not equal finding a new drug. The compound also has to exhibit suitable bioavailability and toxicity profiles. Our hit compound meets the requirements of a ‘validated hit’ as defined by the Medicines for Malaria Venture – but we are a long way from having a drug available on the market.”
“Over the next three years, we hope to optimise the pharmacokinetic properties of our lead compound, and this will require a multidisciplinary team of chemists, pharmacologists, analysts and formulation specialists. We have a number of collaborators who will assist in this development process. In the first instance, a collection of analogues will be prepared, which will be evaluated in an extensive series of in vitro tests – tests that take place in an artificial environment outside a living organism – in an attempt to anticipate the behaviour of the compound in a biological system (i.e. its pharmacokinetic properties). Thereafter the research can progress to testing in small animals, such as mice, followed by larger animals. Only once safety is established in these models do you have a drug candidate, and Phase I clinical trials can be considered for human subjects.”

“To date, the South African research system has not developed a new molecular entity with biological efficacy to the point where it is a genuine clinical candidate, ready for further safety and efficacy evaluation in humans. We think that our compound has the potential to be developed to the candidate stage in the next phase of our research and this would represent a significant achievement.

“Taking this project forward is challenging, but we have been excited and encouraged by our preliminary work. During in vitro tests, one of our compounds was found to be approximately 15 000 times more active than the existing antifolate, cycloguanil, with the majority of compounds showing potent activity against a drug-resistant strain of *Plasmodium falciparum*. Equally important is the lack of acute cellular toxicity.

Although we are very far from having a new, affordable drug on the market, the development of a clinical candidate will greatly contribute to the fight against a disease that predominantly affects the African continent. It would also go a long way in stimulating a local pharmaceutical industry,” Rousseau concludes. – Aida Britz

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