Targeting one enzyme is the key to tackling two tropical diseases

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A way to combat malaria developed by scientists at Imperial College London and the University of York may also be effective against the deadly tropical disease leishmaniasis, new research has shown.

The approach targets a crucial enzyme that causes the parasite to shut down and eventually die following infection. In the latest research – the cover story in this month's *Chemistry & Biology* – the team from Imperial's Department of Chemistry, together with colleagues in the Centre for Immunology and Infection at York, found that blocking the same enzyme in the Leishmania donovani parasite also has a devastating effect on this pathogen.

Leishmaniasis is a tropical parasitic disease spread by sand flies when they feed on human blood, with around 300 million people at risk of infection across north Africa, southern Europe, the Middle East, the Indian sub-continent and Central and South America. The most deadly form of the disease is caused by the parasite Leishmania donovani and kills 30,000 people each year.

"There are many groups around the world working on malaria, but there is much less activity on leishmaniasis, despite it causing a high burden in disadvantaged communities," says Professor Ed Tate, who led the research at Imperial. "The drugs currently available have problems with toxicity and resistance, as well as being expensive."

The enzyme NMT, central to numerous crucial protein functions, was

first identified as a target for drug development in leishmaniasis by Professor Deborah Smith, then at Imperial College and now at the University of York.

"Using molecular genetics, we demonstrated that Leishmania parasites cannot survive in the absence of NMT and subsequently identified small molecule inhibitors that can kill these infective pathogens".

In 2013, research by Professor Tate's group, reported in *Nature Chemistry*, showed that NMT is also central to cellular function in the malaria parasite. They also designed a number of different molecules to inhibit the enzyme, which prevented the parasite from multiplying and extended the lifespan of infected mice.

In this latest study, the team identified which proteins in the Leishmania parasite were affected by the enzyme, and then quantified the effect that NMT inhibitor molecules had on these proteins.

"Relatively little was known about these molecular pathways in this parasite and this rigorous approach allowed us to really dig down to find out more about how it works" said co-author, Dr Megan Wright.

"NMT is a very central drug target," continued Professor Tate. "If you stop it from working, the whole parasite shuts down and dies. We now have the evidence that links the drug-like compounds to their effect on the enzyme and the death of the parasite. We had long suspected that inhibiting this enzyme could be key to tackling other devastating parasitic diseases, so it's particularly pleasing that this seems also to be the case for leishmaniasis."

The team intends to further improve its drug compound portfolio ahead of animal trials, which they hope will take place within 3 years.

Provided by University of York