Research on vitamins could lead to the design of novel drugs to combat malaria

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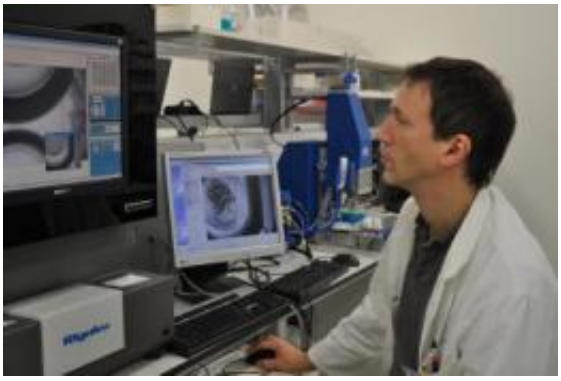

This is Dr. Ivo Tews at the Rigaku Imager for Crystallization Plates. Credit: University of Southampton

New research by scientists at the University of Southampton could lead to the design of more effective drugs to combat malaria.

The research will enable scientists to learn more about the nature of the enzymes required for vitamin biosynthesis by the malaria causing pathogen *Plasmodium*. Vitamins are essential nutrients required in small amounts, the lack of which leads to deficiencies. Many pathogenic microorganisms produce vitamins, and these biosynthetic pathways may provide suitable targets for development of new drugs.

Indeed antifolates targeting vitamin B9 biosynthesis of the malarial parasites have been proven valuable chemotherapeutics for the treatment

of malaria, one of the most devastating infectious diseases leading to nearly 250 million cases worldwide and about 1 million deaths annually. Vitamin B6 biosynthesis of the parasite has been discussed as a drug novel target.

A major factor hindering malaria control is the high degree of resistance developed by *Plasmodium* species against currently available drugs. Hence, there is still an urgent need for the identification of novel drug targets as well as antimalarial chemotherapeutics.

Using the University's Southampton Diffraction Centre, researchers have now been able to describe the malarial enzymes responsible for Vitamin B6 biosynthesis with atomic 3D structures. Vitamin B6 biosynthesis is a highly organised process involving an enzyme complex of 24 protein subunits. The assembly from individual proteins was studied by electron microscopy in collaboration with the Boettcher group at the University of Edinburgh.

Dr Ivo Tews, Lecturer in Structural Biology at the University of Southampton, says: "The structural studies explain how these vital enzymes are activated and show the substrate of vitamin B6 biosynthesis bound to give insights into the chemistry of PLP biosynthesis. The enzyme complex has a fascinating internal tunnel for the transfer of reactive reaction intermediates. The studies also discovered an unexpected organisation of enzyme complexes into fibres.

"The new data are a starting point for the development of specific inhibitors that target either the enzyme's active sites or the assembly of the proteins into functional complexes."

The research, which is an EU F6 funded programme for two years, is published in the latest issue of the journal, *Structure*.