Poster Presentation

MS53.P04

Overcoming drug-resistant malaria through rational drug design in cytochrome bc1

M. Capper[1], P. O'Neill[2], G. Biagini[3], S. Hasnain[1], S. Antonyuk[1]

[1]Unviersity of Liverpool, Institute of Integrative Biology, Liverpool, United Kingdom, [2]Unviersity of Liverpool, Department of Chemistry, Liverpool, United Kingdom, [3]Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Over three billion people live in regions affected by malaria and there are over one million deaths each year [1]. Malaria is caused by the Plasmodium parasite and various drugs are currently used in both treatment and prophylaxis but resistant strains are rapidly emerging. One of the most commonly used anti-malarial drugs is Atovaquone, a hydroxynapthoquinone that is currently used in combination with Proguanil and sold as Malarone™. Atovaquone targets cytochrome bc1 (Complex III, ubiquinol-cytochrome c oxidoreductase), a multi subunit electron transfer protein complex embedded in the inner mitochondrial membrane [2]. Drug resistance rises through a single point mutation in cytochrome b at the Qo site, one of two quinone binding sites. By visualising compounds bound to cytochrome bc1 through x-ray crystallography, it may be possible to modify the compounds to both bind stronger and more specifically. We have worked on compounds that recently failed phase I clinical trials due to cross-reactivity with human cytochrome bc1 [3]. Our structural studies have shown that these compounds appear to bind at the Qi site, which would overcome current drug-resistant strains. Further work here could produce a novel class of anti-malarial drug.

[1] *World Health Organisation, World Malaria Report 2012,* ***[2]*** *M. Kor, N. Che, B. Kot, et al Antimicrobial Agents and Chemotherapy, 2000, 44, 2100-2108,* ***[3]*** *V. Bar, N. Fis, N, G Bia et al Current opinion in chemical biology, 2010, 14, 440-446*

Keywords: Malaria, Cytochrome, Drug-design