Drug repositioning as a route to fast-track anti-malarial drug discovery

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Drug repositioning refers to the usage of existing drugs in diseases other than those it was originally used for. The singular advantage of adopting a repositioning strategy which screens patent expired drug libraries is that the compounds screened are already known to be bioactive and safe for use in humans, significantly reducing the time and cost involved in drug development. Varying degrees of drug resistance has been reported in all currently used anti-malarials, necessitating urgent measures to accelerate the discovery pipeline for this devastating disease. Repositioning strategies are aptly placed to yield not only novel potent monotherapy options, but also synergistic partners for combination therapy to prolong the shelf life of the current frontline antimalarial drugs. We propose a chimeric approach using a repositioning strategy for initial discovery and rational drug design for second-phase lead optimization, in a bid to deliver a safe and affordable anti-malarial therapeutic option. Our work identified Emetine dihydrochloride as a potent anti-malarial in-vitro repositioning screens of ~700 drugs from two patent-expired, FDA approved drug libraries [Matthews 2013]. Despite widespread use as an amoebicide (E. histolytica) for 5 decades, concerns regarding side effects (cardiotoxicity with cumulative dosage, emesis) and the availability of a safer drug (metronidazole), led to curtailment of its use after the 1980’s. A review of existing literature suggests that the side effects are dose dependent. The observed ~1000 fold increased in vitro anti-malarial potency (IC50 1-47 nM for malaria and IC50 25-35 µM for amoebiasis) suggest that dose-dependent toxicity profiles may be quite varied for its repositioned use in malaria. Studies on naturally occurring, structurally similar analogues suggest that minor structural variations result in significant differences in pharmacology, toxicology and selectivity. A recent publication has established the cryo-EM secondary structure for emetine bound to the P. falciparum 80s ribosomal complex, verifying the target binding site of emetine [Wong 2014], enabling rational drug design and molecular modelling to be employed for further lead optimisation. New work in our lab has identified combinatorial partner drugs exhibiting synergistic activity with emetine, thus achieving further dose reduction to improve toxicity profiles.

Biography
Niroshini Nirmalan is a Senior Lecturer and leads the Malaria Drug Discovery Research Group at the University of Salford, UK. After attaining her undergraduate degree at the Faculty of Medicine, University of Colombo, Sri Lanka, she did her MSc and PhD at the University of Salford, Manchester. Her postdoctoral research on developing quantitative proteomic approaches to define the mechanisms of action of anti-folate drugs in malaria was carried out in Prof. John Hyde’s research group at the MIB, University of Manchester. Her current research on Drug repositioning for antimalarial drug discovery is done in collaboration with GSK Tres Cantos and the National Institute for Pharmaceutical research and development (NIPRD, Nigeria).

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