Investigation of the Molecular Target and Resistance Pathways of a New Acridone Derivative with Antiplasmodial Activity

Camila S. Barbosa[1], Sarah El Chamy Maluf[2], Giovana Rossi Mendes[2], Igor M. R. Moura[2], Guilherme E. Souza[1], Talita A. Valdes[2], Vinícius Bonatto[2], Ana C. Puhl[3], Natalia Monakhova[4], Alexander Lepioshkin[4], Renuka Raman[3], Vadim Makarov[4], Thomas R. Lane[3], Guilherme A. S. Campolina[1], Roberto R. M. Barros[1], Ernest D. Benavente[5], Sean Ekins[3], Rafael Victorio Carvalho Guido[2], Anna Caroline Campos Aguiar[1].

[1] Department of Microbiology, Immunology and Parasitology, Federal University of São Paulo, CEP 04023-062, São Paulo, SP, Brazil.

[2] Sao Carlos Institute of Physics, University of Sao Paulo, IFSC – USP, 13566-590, Sao Carlos, SP, Brazil.

[3] Collaborations Pharmaceuticals, Inc., 840 Main Campus Drive, Lab 3510, Raleigh NC 27606, USA.

[4] Research Center of Biotechnology RAS, 33-2 Leninsky prospect, 119071 Moscow, Russia.

[5] Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht 3584 CS, The Netherlands.

Introduction: The control of malaria faces challenges with the emergence of drug-resistant parasites. In this context, our research group has been focused on developing new therapies and evaluating the resisntance mechanism (RM) and mode of action (MoA) of new drug candidates. Acridones is a class of compounds that have been explored for decades in antimalarial development. Preliminary studies identified a promising derivative. Even though initial data suggested that this compound inhibits the bc1 complex, whole-genome sequencing of resistant parasites revealed mutations in genes not directly related to the parasite's mitochondria: glutathione synthetase (GS), T-complex 1 protein epsilon subunit (TCP-1) and lipase putative. Surprisingly, this compound's RM may overlap with artemisinin's partial resistance, since these mutations seem to be involved in REDOX metabolism and protein turnover. **Objectives:** Investigate the molecular target and resistance pathways associated with this derivative. **Methods:** Investigate the speed of action of this compound; identify its peak activity via the stage-specificity assay; metabolomic analysis after exposing the parasite; evaluate the susceptibility of resistant parasites to atovaquone and dihidroartemisinin; investigate whether these mutations confer resistance by inserting them into a sensitive strain. **Results:** The speed of action showed that after 24 h pressure of 10xIC_{50} parasites seem to stall their development for at least 48 h before resuming their development; and this compound has a slow speed of action profile. In addition, this acridone exhibited a peak activity against early and late trophozoites after the stage-specificity assay. **Conclusion:** This acridone has a slow action profile and is more active against the trophozoite stage. Interestingly, 24 h pulse caused a stall in parasite development. Further experiments are underway and we expect that this data will provide more pieces of information to complete this puzzle.