A 3-TIERED SMART SCREENING CASCADE FOR MALARIA

An in vitro platform for use to screen transmission-blocking antimalaria compounds against gametocytes and gametes

BACKGROUND

Malaria is a mosquito-borne disease caused by the protozoan parasite Plasmodium species, with the most severe form caused by Plasmodium falciparum. The disease is transmitted to people by the female Anopheles vector mosquito. This disease is a leading cause of debilitating illness, with over 200 million cases each year from around the world. The disease is widespread in Africa, and over one million people die of malaria every year on the continent, mostly children under the age of five. Sub-Saharan Africa continues to bear >90% of the disease burden. During the years 2000-2015, remarkable progress was made in controlling the disease, but recently there has been an increase in the burden of malaria cases and progress towards elimination has stalled and at the moment, malaria remains a global health threat. In response to this issue, the WHO has developed a Global Technical Strategy for Malaria (2016–2030) that can be used as a framework to guide countries in their efforts to accelerate progress towards malaria elimination. Malaria elimination not only requires continued control of the Anopheles mosquito vectors and the therapeutic use of antimalarial drugs to cure malaria, but in addition, there is a dire need for agents that block the transmission between human and mosquito, thereby disrupting the parasite lifecycle and preventing new malaria infections.

PROJECT DESCRIPTION

The South African Malaria Transmission-Blocking Consortium (SAMTC) was established to identify and develop compounds that will kill the sexual stages of P. falciparum, which are transmitted to the Anopheles vector. The consortium has developed several in vitro assay platforms targeting different biological endpoints to detect activity of compounds against gametocytes and gametes. A standard membrane feeding assay has also been established to evaluate the in vivo effect of compounds against the development of oocysts and sporozoites in African mosquito vectors. A liver-stage assay is also being developed, which will enable the consortium to investigate the complete parasite lifecycle. Clinical isolates from patients with currently-circulating P. falciparum parasite strains provide a resource for evaluating potential resistance against lead compounds.

VALUE PROPOSITION

The SAMTC has designed a unique, 3-tiered smart screening cascade to be used as a road map for screening transmission-blocking antimalarial compounds. The combined expertise within the SAMTC has clearly placed it as a main international role player in the field and a reference for interrogating large compound libraries. The SAMTC has built capacity and trained a core group of young scientists in cutting-edge technologies in the malaria field. In addition, this geographically centralised consortium in a malaria-endemic African country with access to malaria patients and African Anopheles vector species, places the group in the unique position of being able to interrogate all stages of the parasite life cycle. It is anticipated that the SAMTC will contribute significantly to the global malaria elimination agenda by spearheading the identification, prioritisation, and development of a new generation of validated compounds with a target candidate profile (TCP) that will block transmission of the parasite to the vector and prevent the spread of the disease (TCP5).

CURRENT STATUS

- More than 25 000 compounds have been screened from approximately 17 distinct chemical backgrounds (libraries) with potential TCP5 activity.
- The SAMTC contributed towards the description of the first South African (and African) antimalarial compound, MMV390048, with transmission-blocking capacity, which is currently undergoing clinical trials in collaboration with Medicines for Malaria Venture (MMV); and was instrumental in the prioritization of a second back-up pre-clinical candidate.
- The SAMTC has also formalised an active partnership with the University of Cape Town's H3D Drug Discovery Platform, to create a single consortium, the South African Malaria Drug Discovery Consortium, which will be funded through various international partnerships and the SAMRC Strategic Health Innovation Partnership (SHIP).

INTELLECTUAL PROPERTY STATUS & PUBLICATIONS

1. Moyo et al. (2019) Bioassay-guided isolation and identification of gametocytocidal compound from Artemisia afra (Asteraceae). (Accepted, Malaria J).
2. Kumar et al. (2019) Multistage antiplasmodium activity of astemizole analogues and inhibition of hemozoin formation as a contributor to their mode of action. ACS Infect. Dis., Just Accepted Manuscript DOI: 10.1021/acsinfecdis.8b00272 Publication Date (Web): 11 Dec 2018, http://hdl.handle.net/2263/68201
3. Mayoka et al. (2019) Structure-activity relationship studies and Plasmodium life cycle profiling identifies pan-active N-aryl-3-trifluoromethyl pyrido[1,2-a]benzimidazoles which are efficacious in an in vivo mouse model of malaria. J. Med. Chem., DOI: 10.1021/acs.jmedchem.8b01769 Publication Date (Web): 18 Dec 2018
4. de Lange et al. (2018) Synthesis, antimalarials activities and cytotoxicities of amino-artemisinin-1, 2-disubstituted ferrocene hybrids. Bioorg Med Chem Lett. 28, pp. 3161-3163. doi: 10.1016/j.bmcl.2018.08.037. (IF 2.42)
5. Beteck et al. (2018). Accessible and distinct decoquinate derivatives highly active against M. tuberculosis and apicomplexan parasites. Comms. Chem, 1(62) DOI: 10.1038/s42004-018-0062-7
6. Brunschwig et al. (2018) UCT943, a next generation

A 3-TIERED SMART SCREENING CASCADE FOR MALARIA (CONTINUED)

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Plasmodium falciparum PI4K inhibitor preclinical candidate for the treatment of malaria. Antimicrobl. Agents Chemotherapy. Aug 27;62(9). pii: e00012-18, doi: 10.1128/AAC.00012-18 (IF 4.476)

7. Coertzen et al. (2018) Artemisone and artemiside - potent pan-reactive antimalarial agents that also synergize redox imbalance in P. falciparum transmissible gametocyte stages. Antimicrobl. Agents Chemotherapy. August 2018, 65:8, e02214-17. doi: 10.1128/AAC.02214-17 (IF 4.476) (http://hdl.handle.net/2263/66344)
8. Van der Watt et al. (2018) Potent Plasmodium falciparum gametocytocidal compounds identified by exploring the kinase inhibitor chemical space for dual active antimalarials. J Antimicrob Chemotherapy, doi: 10.1093/jac/dky008 (IF: 5.313)
9. Morake et al. (2018) Preliminary evaluation of artemisinin - cholesterol conjugates as potential drugs for treatment of intractable forms of malaria and tuberculosis. ChemMedChem. 2018 Jan 8;13(1):67-77. Doi: 10.1002/cmdc.201700579. (IF 3.225)
10. de Lange et al. (2018) Synthesis, in vitro antimalarial activities and cytotoxicities of amino-artemisinin-ferrocene derivatives. Bioorg Med Chem Lett. 28(3), pp. 289-292. doi: 10.1016/j.bmcl.2017.12.057. (IF 2.42)
11. Harmse et al. (2017) Activities of 11-azaartemisinin and N-sulfonyl derivatives against asexual and transmissible malaria parasites. ChemMedChem. Dec 19;12(24):2086-2093. Doi:10.1002/cmdc.201700599, (IF 3.225)
12. Paquet et al. (2017) Antimalarial efficacy of MMV390048, an inhibitor of Plasmodium phosphatidylinositol 4-kinase.Sci Transl Med. 2017 Apr 26;9(387). pii: eaad9735. Doi: 10.1126/scitranslmed.aad9735.
13. Singh et al. (2017) Antimalarial pyrido[1,2-a]benzimidazoles: lead optimization, parasite life cycle stage profile, mechanistic evaluation, killing kinetics, and in vivo oral efficacy in a mouse model. J Med Chem. 60(4):1432-1448. doi: 10.1021/acs.jmedchem.6b01641. (IF 5.447)
14. Bennett et al. (2016). Plasmodium falciparum infection of laboratory strains of the four major African malaria vector species. NICD Bulletin 14:2
15. Van Voorhis et al. (2016) Open source drug discovery with the Malaria Box compound collection for neglected diseases and beyond. PLOS Pathogens 2016 July 28 https://doi.org/10.1371/journal.ppat.1005763
16. Le Manach et al. (2016). Straightforward conversion of decoquinate into inexpensive tractable new derivatives with significant antimalarial activities. Bioorg Med Chem Lett. 26(13):3006-9. doi: 10.1016/j.bmcl.2016.05.024. (IF 2.42). (http://hdl.handle.net/2263/53594)
17. Birkholtz et al. (2016) Discovering new transmission-blocking antimalarial compounds: challenges and opportunities. Trends Parasitol. 2016 May 18. 32(9):669-81, doi: 10.1016/j.pt.2016.04.017. Invited review, (IF 6.042)
18. Moyo et al.(2016) In vitro inhibition of Plasmodium falciparum early and late stage gametocyte viability by extracts from eight traditionally used South African plant species. J Ethnopharmacol. 2016 Mar 16. 185:235-42 doi: 10.1016/j.jep.2016.03.036. (IF 2.998), (http://hdl.handle.net/2263/55666)

OPPORTUNITIES

The SAMTC is looking for partnerships for the screening and identification of transmission-blocking antimalarial compounds.

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