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Editorial: Advances in anti-malarial drug discovery

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Editorial on the Research Topic
Advances in anti-malarial drug discovery

Malaria remains one of the most important infectious diseases, killing ~3 million people and annually causing illness in ~500 million people. A protozoan parasite, *Plasmodium falciparum*, causes severe malaria. Two of the most widely used antimalarial drugs, chloroquine (CQ) and sulphadoxine–pyrimethamine (SP), fail in most malaria-endemic regions. Malaria blood-stage infection also generates gametocytes (sexual stages), which are infectious to mosquitoes and lead to oocyst formation containing sporozoites. Sporozoites invade salivary glands and are introduced into humans through mosquito bites. New drugs are desperately needed to fight malaria. Traditional methods for drug development have yielded only a handful of drugs. In this challenging situation, sustained efforts are necessary to identify and develop new antimalarials. New antimalarial drugs should have rapid efficacy, minimal toxicity, and low cost. Ideally, new drugs should also be efficacious against drug-resistant strains and cure patients quickly (2–3 days) to ensure better compliance. These drugs should be safe, appropriately formulated, and, most importantly, affordable as malaria is a disease associated with poverty. There is a consensus that drug combinations are essential to combat malaria. Combination drugs offer several advantages over monotherapies, such as lower drug resistance development and better efficacy. The antimalarial drugs presently in use were not developed based on rationally identified targets; thus, an enormous opportunity exists to develop new drugs based on known targets and known mechanisms of action.

Accordingly, the aim of this Research Topic of Frontiers in Drug Discovery, "*Advances in Anti-Malarial Drug Discovery*," is to collect the latest research on the Research Topic focused on:

- Identification of novel targets
- Multi-stage active antimalarials
- Identification of novel chemical scaffolds
- Drugs with longer retention in the body and single-dose cures
- Repurposing of existing drugs.

This Research Topic aims to provide an overall insight into the novel or recent progress in anti-malarial drug discovery, highlighting novel strategies, current challenges, latest discoveries, recent advances, and future perspectives in the field. The contributions

covered in this Research Topic are summarized underneath, arranged in alphabetical order of the corresponding authors' last names.

Malaria disease is a global burden, and increasing resistance to available antimalarials is a significant concern, warranting new research and innovations toward improved therapies. A review by Reghunandanan and Chandramohaandas, "*Chemically induced phenotypes during the blood stage development of Plasmodium falciparum as indicators of the drug mode of action*," summarizes the various life-stage events of the malaria parasite during *in vitro* development, which different classes of small molecules can target. The authors also describe various chemically induced phenotypes and methods to ascertain and validate drug-induced changes to derive early insights into which cellular mechanisms are affected. The authors propose that thorough documentation of the morphological and physiological changes across blood-stage development provides a feasible method to apply a variety of cell biological and imaging tools to capture the cellular consequences of small-molecule treatment systematically. This approach can facilitate the identification of molecules with unique inhibitory potential and provide information on phenotypic outcomes to better understand the specific modes of action and cellular targets.

Plasmodium encodes larger proteins than its eukaryotic counterparts, with homology regions present in the C-terminus of the protein. In contrast, the function of unusual extensions in the N-terminus remains mostly elusive. Tehlan et al., in the review "*Targeting proteases and proteolytic processing of unusual N-terminal extensions of Plasmodium proteins: parasite Peculiarity*," discuss in detail an unusual phenomenon observed in the parasite proteome N-terminal extensions in proteins and highlight that the proteases that may be involved in their processing events might be potential candidates to target the malaria parasite. The plausible functions and prevalence of these extensions through the parasite evolution are also mentioned. The authors hypothesize that these extensions, propagated via the energy-consuming cellular processes in the otherwise host-dependent obligate parasite, benefit the parasite in ways that are yet to be explored.

The abundance of unusual extensions in the *N*-terminal region of proteins in the Plasmodium proteome is thought provoking. Interestingly, most of these extensions comprise asparagine repeats. These repeats, accounting for 25% of the Plasmodium proteome, are known to have expanded evolutionarily and undergone positive selection pressure.

Prashar et al., in the article "*The landscape of nature-derived antimalarials-potential of marine natural products in countering the evolving Plasmodium*," discuss the significant antimalarial potential of marine-derived natural products extracted from diverse biota, including sponges, bacteria, sea hare, and algae, etc. Bioassay-guided fractionation of raw extracts from marine organisms for lead identification and further structural characterization of purified compounds compose a sustainable marine-derived drug discovery pipeline against malaria. The discovery of novel marine-derived antimalarials may offer new scaffolds, leading to the development of a new generation of synthetic antimalarials. This review has collated and summarized marine-derived antimalarial compounds, and specific emphasis has been placed on the global advancements in identifying marine therapeutics from diverse biota. Marine-derived bacteria have become the richest source of lead antimalarials with IC_{50} values in the nM range.

Antimalarial chemotherapy is becoming difficult due to the emergence of multidrug-resistant *P. falciparum* parasites. Ionophores display antiplasmodial activity by intercalating with the parasite membrane and exchanging ions, leading to increased cytosolic ion concentration and alteration in pH, causing parasite death. Rajendran and Gurukkalot, in the article "*In vitro drug interaction of Ionophores with Artemisinin and Chloroquine against P. falciparum blood-stage infection*," demonstrate the potential interactions of carboxylic ionophores with the standard antimalarial drugs artemisinin (ART) or chloroquine (CQ). Combining artemisinin with ionophores showed significant additive interaction. A combination of chloroquine with ionophores showed slight synergism to additive interaction. None of the drug combinations displayed an antagonistic effect, indicating the usage of ionophores in combination therapy to treat drug-resistant malarial infections.

As a concluding remark, this Research Topic exemplifies recent progress in the efforts toward developing new chemotherapy, potential targets for discovering new drugs, and repurposing old ones. We would like to thank all the contributors especially.

Author contributions

AS: Conceptualization, Formal Analysis, Funding acquisition, Writing–review and editing. BR: Validation, Writing–review and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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