

# Drug Discovery in Malaria using the cAMP Signaling Pathways

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## DESCRIPTION

Malaria is one of the most significant tropical diseases that affect humans, which is brought on by several Plasmodium species, which are protozoan parasites from the apicomplexa. The "apicoplast" is a plastid-like structure found in the apicomplexan parasite genera Plasmodium, Toxoplasma, and Cryptosporidium, which are responsible for the diseases malaria, toxoplasmosis, and cryptosporidiosis, respectively. Despite significant efforts and improvements in drug discovery, there are still few treatments for these undertreated diseases, partly due to the emergence of drug resistance to commercially available drugs. It's crucial to establish a successful center that is committed to discovering new paths with novel treatment targets. Apicomplexan parasites are a desirable source for the creation of novel medications because to the different cAMP-regulated pathways seen in them. Here, the most notable differences from the human host are outlined, with a focus on Plasmodium.

At a time when conventional treatment is losing its efficacy, the identification of pathways with novel targets is essential for the management and eradication of important global parasitic diseases. An effective tool in this case is the non-canonical cAMP-regulated pathways of the apicomplexan parasites that cause toxoplasmosis, cryptosporidiosis, and malaria. This discussion illustrates several methods for resolving the problem.

- Due to the lack of canonical G-proteins and G Protein-Coupled Receptors (GPCRs) in these parasites compared to the mammalian host, inhibition of the host proteins may reduce the parasite load. For all three genera of apicomplexan parasites to survive, the human host's canonical, cAMP-regulated pathways are crucial.
- Inhibiting the Rap1 protein in the guanine nucleotide exchange pathway is a promising method for preventing the parasite's invasion and escape.
- Out of the secondary effector proteins, or the family of ACG kinases, Kinase G is the most promising target in *Plasmodium* because it plays essential regulatory roles throughout the whole parasite life cycle. An inhibitor with an imidazopyridine lead structure has already demonstrated that it

satisfies the WHO criterion that a single treatment eradicates the parasite in each embryonic stage.

• Small Ras GTPases from all three genera, which interact with specific host enzymes to speed up parasite invasion and proliferation, in the development of new drugs has not yet been adequately explored.

### Plasmodium

The most important member of the apicomplexa is *Plasmodium*, the deadly parasite that causes malaria. After infecting the human host, the malaria parasite must develop in two different environments, namely the preerythrocytic stage in the liver and the erythrocytic blood stages. The mosquito then transitions into its sexual stage, which results in the development of ookinetes in its midgut, which then develop into an oocyst that produces sporozoites in the salivary glands. The parasite can only react fast to these developmental changes through signaling pathways. Research on apicomplexan parasites has not advanced as swiftly as that on cyclic nucleotide regulated pathways in humans due to the lack of available genomic data. Yet, recent advances in genome sequencing have revealed that the elements of their cyclic nucleotide pathways are dissimilar.

#### Toxoplasma

Toxoplasmosis is brought on by the typical protozoan parasite Toxoplasma gondii. It has an impact on 30% of people. Three different developmental forms-the oocyste. tachyzoite, and bradyzoite-appear throughout its life cycle. The transmission is done through cat feces, which are where the oocysts are discovered. Pregnant women who contract congenital toxoplasmosis, brought on by the parasite's quickly replicating tachyzoite form, have tissue damage and fetus infection. Depending on the host's immune response, tachyzoites can change into bradyzoites, especially in muscles and the Central Nervous System (CNS). Yet, certain tachyzoites have the capacity to resist the host's immune response and revert to bradyzoites. Bradyzoites can be eaten in meat, and when they are ingested by a human host, they change into tachyzoites.

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Received: 01-Mar-2023, Manuscript No. JCS-23-23116; Editor assigned: 03-Mar-2023, PreQC No. JCS-23-23116 (PQ); Reviewed: 17-Mar-2023, QC No. JCS-23-23116; Revised: 24-Mar-2023, Manuscript No. JCS-23-23116 (R); Published: 31-Mar-2023, DOI: 10.35248/2576-1471.23.08.329

Citation: Salmona A (2023) Drug Discovery in Malaria using the cAMP Signaling Pathways. J Cell Signal. 8:329

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#### Cryptosporidium

Human cryptosporidiosis, a self-limiting diarrhea in healthy people, is caused by both *Cryptosporidium* hominis and *Cryptosporidium* parvum, which can infect both humans and animals. Immunocompromised people, such as those with HIV-1 infection or children, might have severe diarrhoea with consequences on the biliary tree and the respiratory organs. The sporulated oocysts are expelled through the respiratory system or in the feces to start the life cycle. After ingestion or inhalation, sporozoites are secreted and parasitize epithelial cells. Before the sexually mature micro- and macrogamonts create the oocyste, asexual reproduction (schizogeny or merogony).