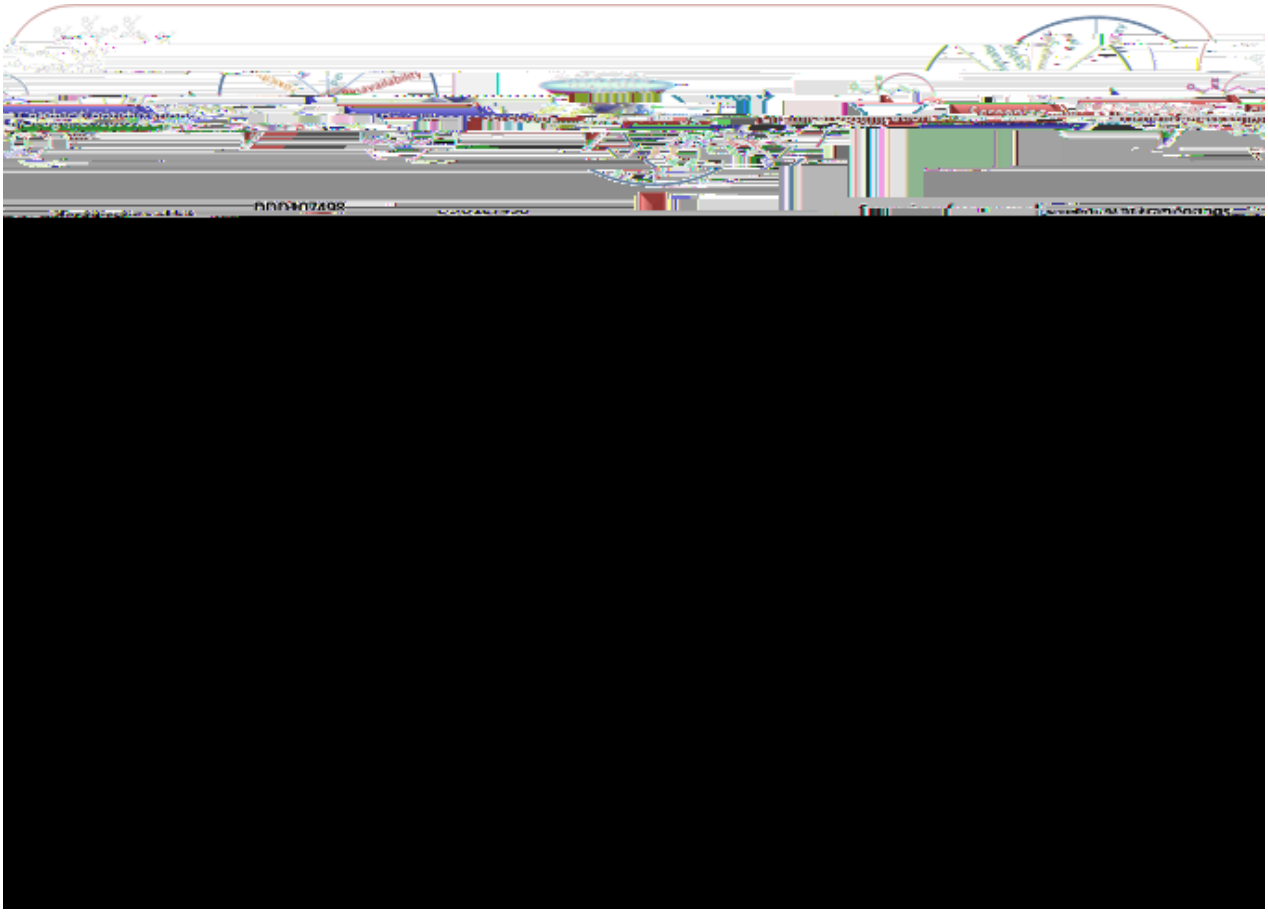

Figure 1: Schematic representation of (A) different processes involving development and (B) mechanism of action and properties of the new antimalarial compound DDD107498.

Further, stage-specificity study of *P. falciparum* using synchronized cultured in SCID mouse model revealed the fatal activity of the compound in each stage of the malaria parasite. At the concentration of 4 nM for 24 hours, the compound ceased production of normal trophozoite from ring stage, prevented schizont formation from trophozoites, and ring formation from schizont with reduction of parasite, providing evidence of its efficacy to hinder growth and development of all asexual blood stages of the parasite. Furthermore, the compound interrupted the life cycle of parasite at multiple stages (pre-erythrocytic, erythrocytic and post erythrocytic), meaning greater chemo-protection and transmission blockage characteristics. Specifically, it was found that the molecule can act on the intra-hepatocyte parasites, thereby could be considered as a chemo-protective agent as well as gametocytes-disrupting, blocking malaria transmission process. To this respect, the compound was found to be more efficient than currently used atovaquone along with proguanil as a chemo-protective agent and also provides protection during intermittent infection. The chemo-protective potential of the compound was assessed in vivo by treating the mouse with DDD107498 at 3 mg/kg. Two hour later, the mouse was infected with *P. berghei* and there was no sight of parasitemia after 30 days. This demonstrates that the compound is a potent chemo-protective agent. In addition, the team performed standard membrane feeding assay and used *P. berghei* infected mouse model to unravel its role and strong potential to block transmission.

Since the important aspect of drug development lies in the evaluation of toxicity of the drug to humans, various experiments were performed to evaluate toxicity of the newly developed compound DDD107498. The concentration at which the compound reduces maximum parasitemia was exposed to human cell lines (hepatocytes and MRC5) and it was found that the compound was non-toxic to human cell even at higher concentration. Also, it neither caused excess inhibition nor induction to the activity of Cytochrome P450 isoforms, therefore, probability of drug-drug interaction was fairly negligible. This is because, Cytochrome P450 and its isoforms serve important role in drug metabolism process and its excess inhibition or induction hampers the drug efficacy. In addition, very low inhibitory response to other ion channels, non-mutagenic characters and long half-life of DDD107498 have made it fairly promising single-dose cure that can provide once-in-a-week chemo-protection against malaria parasite infection.

With the knowledge on the strong potentiality of the DDD107498 compound that can be an effective antimalarial, the research team5 further searched for the target of action of this compound in the malaria parasite *P. falciparum*

Possession of good pharmacokinetics property and (vii) Global

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