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 Herz Global Impact Award



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Deciphering the mechanism of action of β -carboline derivatives – A novel class of antimalarials

Malaria is a devastating disease that caused approximately 619,000 deaths in 2021 worldwide. Cases of malaria have increased from previous years in part by the quick development of resistance to current antimalarials. Due to the rising resistance to current antimalarial drugs such as chloroquine and artemisinin, there is an urgent need to discover and develop new drugs that engage new targets in the malaria parasite. This research focuses on a novel antimalarial called PRC1584.

Malaria and its Life Cycle

- Malaria is a life-threatening disease caused by *Plasmodium* parasites that are transmitted to humans when infected female *Anopheles* mosquitoes take a blood meal.

Malaria and PRC1584

PRC1584
 $EC_{50} = 50 - 100 \text{ nM}$
 US Non-provisional patent No. PCT/US2021/024542

Artemisinin
 + ART derivatives like Dihydroartemisinin (DHA), artesunate, and artemether

Early Lead Criteria for Antimalarials

Criteria	PRC1584
Global Health Innovative Technology (GHIT) Fund and Medicines for Malaria Venture (MMV) devised the following disease-specific criteria for early leads for malaria.	PRC1584
EC_{50}	<100 nM for sensitive and multidrug-resistant strains of plasmodium spp. ✓
Selectivity Index	>100 in mammalian cells ✓
In vivo efficacy	When administered orally in blood stages of infection: Clearance at a dose that eradicates 90% of the target (<50 mg/kg) (four doses over 4 days) ✓
Irresistible	Unable to generate resistance ✓

Artemisinin Induced Quiescence

- Quiescence - is the altered ring stage development in artemisinin-resistant *P. falciparum* in which ring stages persist for extended periods of development **in the absence of drug**.

Quiescence Survival Assay

Does 1584 kill DHA-induced quiescent ring stage?

Short exposure to 1584 kills both proliferating and DHA-induced quiescent ring stages.

Chemoproteomic approaches for target deconvolution

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