Lipid kinase enters the malaria stage

By Benjamin Boettner, Associate Editor

A Novartis AG–University of California, San Diego–led consortium has identified a new class of antimalarials that, unlike marketed drugs, eliminates *Plasmodium* at all stages of its infection cycle.¹ The pharma is developing derivatives of the lead inhibitor with improved drug-like properties.

Plasmodium's life cycle consists of several distinct stages. Mosquito-injected sporozoites rapidly populate liver cells, in which they either proliferate and produce merozoites that emerge in the bloodstream or enter a dormant phase as hypnozoites in the liver.

Emerging merozoites can undergo several cycles of asexual multiplication in the blood, resulting in thousands of infected red blood cells and causing malaria symptoms. Merozoites also can develop into sexual-stage gametocytes, which are taken up by mosquitoes and ultimately give rise to a new generation of sporozoites to be injected into the next host.²

Latent hypnozoites, on the other hand, can linger in the liver for long periods of time, causing disease relapse sometimes years after the initial infection when mobilized back into the bloodstream as merozoites.

Thus, eradicating malarial disease requires *Plasmodium* to be targeted at replicating stages in liver and blood, dormant stages in liver and sexual stages in blood.

Marketed drugs offer an either-or proposition. Chloroquine and artemisinin and its derivatives are only effective against the blood stages of the parasite. Marketed artemisinin derivatives include Novartis' Coartem artemether/lumefantrine, ASAQ artesunate/amodiaquine from Sanofi and Eurartesim dihydroartemisinin/piperaquine from Sigma-Tau Group.

Only one marketed drug eliminates liver-stage dormant hypnozoites: the generic 8-aminoquinoline primaquine. Primaquine also has very weak activity against the blood stages of *Plasmodium*, but it causes significant side effects.

Now, a Novartis-UCSD consortium has determined that inhibiting a single *Plasmodium* kinase—*Plasmodium* phosphatidylinositol 4-kinase III β (PI4KIII β)—can interfere with all stages of the *Plasmodium* life cycle.

Using a cell-based screen, the researchers identified a series of imidazopyrazines that were active against drug-sensitive and drug-resistant asexual blood-stage *Plasmodium*.

A lead imidazopyrazine derivative inhibited both the asexual and

sexual blood stages of different *P. falciparum* and *P. vivax* strains *in vitro* and in mice. The compound also showed strong activity against liver-specific hypnozoites in models of dormant *Plasmodium* infection.

Based on these results, the team hypothesized that the compound's target was essential to all stages of the parasite's life cycle. Genetic studies revealed that the target was PI4KIII β .

Francisco Javier Gamo Benito told SciBX that the target's key role in lipid sorting and signaling "explains the diversity of stages of the *Plasmodium* life cycle that are affected by PI4KIII β inhibitors."

Gamo Benito is director of R&D for alternative discovery and development at GlaxoSmithKline plc's malaria discovery performance unit. GSK markets Malarone atovaquone to inhibit *Plasmodium* pyrimidine synthesis and has the malaria vaccines GSK257049 and PlaMaVax in Phase III and Phase II trials, respectively. The company also has the 8-aminoquinoline tafenoquine (SB 252263) in Phase II testing and the electron transport inhibitor GSK932121 in Phase I trials.

Although *Plasmodium* PI4KIII β shares 43% identity with the human kinase catalytic site, the team's lead compound had 1,000-fold selectivity for *P. falciparum* or *P. vivax* kinases over the human kinase. It also inhibited PI4KIII β with IC₅₀ values in the low nanomolar range.

Results were published in *Nature*. The team was led by the Genomics Institute of the Novartis Research Foundation, the Novartis Institute for Tropical Diseases and UCSD.

According to co-investigator Thierry Diagana, head of the Novartis Institute for Tropical Diseases in Singapore,

"imidazopyrazine compounds have a unique spectrum of activities across the *Plasmodium* life cycle. There are no previously reported compounds that can interfere with all stages of the parasite in its host."

"Our work shows that PI4KIII β would be worthwhile pursuing using target-based drug discovery," added co-investigator Elizabeth Winzeler, a professor of pediatrics and director of translational research at the UCSD Health Sciences Center for Immunity, Infection and Inflammation.

The resistance question

Diagana said that Novartis is selecting optimized derivatives of the imidazopyrazine and evaluating oral availability, stability, safety and other properties typically required for an antimalarial drug.

"The real jewel in the crown would be to see how data on hypnozoite relapse actually translate *in vivo*," said Timothy Wells, CSO at the Medicines for Malaria Venture.

Although it is clear that the next step will be to show efficacy in a nonhuman primate model of malaria, an outstanding issue is the potential for emerging resistance.

"As is the case with other antimalarial drugs, the biggest problem is the rapidity with which that resistance occurs in asexual blood stages. Blood stages outnumber other life cycle stages by far and are where resistance and selection are proceeding the fastest," said Louis Miller, chief of the malaria cell biology section at NIH's National Institute of Allergy and Infectious Diseases.

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**—Elizabeth Winzeler,
University of California, San Diego**

Both Diagana and Miller said that it would be important to incorporate any new clinical candidates into combination therapies to reduce the likelihood of resistance emergence.

Novartis has filed for patents covering the chemical matter of imidazopyrazine compounds. The compounds are not available for licensing.

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