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Antimalarials: Pre-clinical development update

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ABSTRACT

Diverse strategies exist for the development of novel antimalarials to tackle the increasing incidence of artemisin resistance. New molecules have been developed which hold a promise to cater to this unmet need. We discuss few drugs currently under pre-clinical development that have shown encouraging results.

Key words: Artemisin, Resistance, Malaria, Novel drugs

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INTRODUCTION

The challenge of the antimalarial drug development is to deliver a drug that should: (i) address drug-resistance issues, (ii) have a rapid onset of action, (iii) be safe, especially in children and pregnant women, and (iv) cure malaria in a single dose (v) identify novel targets. Artemisinin-based combination therapies (ACTs) are currently gold standard in treating uncomplicated malaria, have an inherent issue of emerging resistance. To tackle this problem, sophisticated cellular and phenotypic screening methods have identified drug candidates active against different stages of the parasites life cycle in recent years (Table 1). We discuss few of such innovative strategies currently under preclinical development.

PRE CLINICAL DEVELOPMENT UPDATE

The mitochondrial enzyme dihydroorotate dehydrogenase (DHOD) has been recognized as a potential antimalarial target, as it catalyzes the fourth step in the essential *de novo* pyrimidine biosynthesis pathway.[1,2] A new chemical class, the triazolopyrimidines, has been identified with potent activity in whole-cell assays (*P. falciparum* IC_{50} = 79 nM) and >5000 fold specificity for parasite over human DHOD, though this class was inactive in the *P. berghei in vivo* model. The molecules underwent series of chemical modifications, and a potent lead discovered that had an IC_{50} of 40–50 nM against drug-sensitive and drug-resistant *P. falciparum,* including those resistant to chloroquine, atovaquone, and the antifolate, pyrimethamine.[3] A drug canidiate, DSM265, showed similar potency as chloroquine in mouse models, and is now the first DHOD inhibitor to enter pre-clinical trials.[4]

In-silico molecular docking approach was used to identify potential inhibitors that disrupt the interaction between the carboxy terminal tail of myosin A and the myosin tail interacting protein (MTIP) of the malaria parasite. This interaction is required for erythrocyte invasion. Optimization of a urea-pyrazole scaffold has yielded a molecule, 21A092, which targets the protein, has now advanced to preclinical studies.[5]

Synthetic peroxides are proving to be useful substitutes for artemisinin. The first-generation ozonide OZ277, known as arterolane, has been found to inhibit the growth of chloroquine-resistant (K1) and chloroquine sensitive (NF54) parasite strains with an IC50 = 1.6–1.8 nM. In 2012, the combination of arterolane maleate and piperaquine phosphate was released as a 3-day treatment in India. The second-generation peroxide OZ439

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Table 1: Summary of novel antimalarial compounds under preclinical development

Compound	Chemical class	Target or MOA	Therapeutic activity
DSM265	Triazolopyrimidine	DHOD	*Chemotherapeutic*
21A092	Pyrazole	Unknown	*Chemotherapeutic*
MMV390048	Aminopyridine	Unknown	*Chemotherapeutic*
P218	Diaminopyridine	DHFR	*Chemotherapeutic; Prophylactic*
RKA182	1,2,4,5-tetraoxane	Hemoglobin digestion	*Chemotherapeutic*
ELQ-300	Quinolone-3-Diarylether	Cytochrome bc1	*Chemotherapeutic; Transmission blocking; Prophylactic*
BCX4945	Immucillin-G	PNP	*Chemotherapeutic*
NPC-1161B	8-aminoquinoline	Unknown	*Chemotherapeutic; Transmission blocking; Prophylactic*

DHOD: Dihydroorotatereductase; DHFR: Dihydrofolatereductase; PNP: Purine nucleoside phosphatase; MOA: Mechanism of action

(EC50 = 3.4–4.0 nM) featuring an 80- aryl rather than an 80-alkyl group causing higher stability of the O–O bond towards Fe(II) increasing by 50-fold, presumably because of steric reasons, is now in Phase IIa studies.[6,7] Tetraoxanes (also stabilizes O–O bond), as was employed in the drug development candidate RKA 182, has displayed IC50 values of 4.9 nM against the *P. falciparum* 3D 7 strain and of 1.9 nM against the K1 strain (chloroquine sensitive and -resistant, respectively). It reduced *P. berghei* parasitemia in mice to undetectable levels 24 hours after treatment. This compound is currently in preclinical trials and although it has greater stability than OZ277, its antimalarial activity is inferior to OZ439.[8,9]

Phenotypic whole-cell screening method has revealed a 2-aminopyridine class of small molecules as a good starting point to develop new a derivative, MMV390048, which lacked cross-resistance with current drugs used to treat malaria, and has a potential ability to block all life cycle stages of the malaria parasite. Both genomic and chemoproteomic studies have identified a kinase of the *Plasmodium* parasite, phosphatidylinositol 4-kinase, as the molecular target of MMV390048. This compound was efficacious against all *Plasmodium* life cycle stages, apart from late hepatic hypnozoites. Efficacy was shown in the humanized *Plasmodium falciparum* mouse model, and modest reductions in mouse-to-mouse transmission were achieved in the *Plasmodium berghei* mouse model.[10,11]

P218, a dihydrofolatereducatse inhibitor (DHFR) inhibitor has been found to be active against all clinically relevant mutations of the parasite. It combines the pyrimidine ring of pyrimethamine which brings potency, and the linker of the DHFR inhibitor WR99210, which tolerates mutations due to its flexibility. P218 is more potent than pyrimethamine against DHFR in the wild-type strain TM4 (IC50 = 4.6 and 58 nM, respectively) as well as in the quadruple mutant strain V1/S (IC50 = 56 and >100,000 nM, respectively). It has an activity against quadruple mutant P. falciparum in mice, with an ED50 = 0.3 mg/kg/day, orally.[12,13]

The 8-aminoquinoline (8AQ) class of anti-malarial compounds is unique due to the efficacy against relapsing forms of malaria. This activity is a result of the anti-hypnozoite activity. Paired along with the gametocidal activity of primaquine (PQ), 8AQs make a class attractive for mass administration in efforts towards malaria eradication.Tafenoquine (TQ) is an 8-aminoquinoline (8AQ) currently in late stage development as an anti-malarial prophylactic agent. NPC-1161B is another promising 8AQ in late preclinical development.[14,15]

ELQ-300 is an endochin-like quinolone and the first in a new class of antimalarials known as quinolone-3-diarylethers. It acts as an inhibitor of the mitochondrial cytochrome bc1 complex (complex III in the electron transport chain). In preclinical studies with mice, it was found to be highly active against all life cycle stages of the malaria parasite. It targets the liver and blood stages of Plasmodium falciparum, as well as the forms that are crucial to transmission of disease: gametocytes, zygotes, and ookinetes.[16,17]

Blocking of purine nucleoside phosphorylase (PNP) has been found to kill cultured parasites by purine starvation, since *Plasmodium* species are known to be purine auxotrophs. DADMe-Immucillin-G (BCX4945) is a transition state analogue of human and *Plasmodium* PNPs, binding with picomolar affinity. Metabolite analysis has demonstrated that PNP blockade inhibits purine salvage and polyamine synthesis in the parasites. The efficacy, oral availability, chemical stability, unique mechanism of action and low toxicity of BCX4945 demonstrate potential for combination therapies with this novel antimalarial agent.[18,19]

CONCLUSION

It is an exciting time for malaria drug discovery, and the drug pipeline looks robust. The combination of new and innovative screens to identify compounds with broad-range activity is hoped to yield new insight into chemicals with broad-range activity.

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