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Review Article

Drug Development Strategies for Malaria: With the Hope for New Antimalarial Drug Discovery—An Update

Swaroop Kumar Pandey,[1] **Uttpal Anand**,[2] **Waseem A. Siddiqui**,[3] **and Renu Tripathi**[4]

[1]*Department of Life Sciences, The National Institute for Biotechnology in the Negev, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel*
[2]*Department of Life Sciences, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel*
[3]*Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh 202001, Uttar Pradesh, India*
[4]*Department of Molecular Microbiology and Immunology, CSIR-Central Drug Research Institute, Lucknow 226031, Uttar Pradesh, India*

Correspondence should be addressed to Swaroop Kumar Pandey; pandey@post.bgu.ac.il

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Malaria continued to be a deadly situation for the people of tropical and subtropical countries. Although there has been a marked reduction in new cases as well as mortality and morbidity rates in the last two decades, the reporting of malaria caused 247 million cases and 619000 deaths worldwide in 2021, according to the WHO (2022). The development of drug resistance and declining efficacy against most of the antimalarial drugs/combination in current clinical practice is a big challenge for the scientific community, and in the absence of an effective vaccine, the problem becomes worse. Experts from various research organizations worldwide are continuously working hard to stop this disaster by employing several strategies for the development of new antimalarial drugs/combinations. The current review focuses on the history of antimalarial drug discovery and the advantages, loopholes, and opportunities associated with the common strategies being followed for antimalarial drug development.

1. Introduction

Malaria continues to be a major public health concern and has a significant global impact. Malaria is a vector-borne disease caused by certain species of unicellular eukaryote *Plasmodium* spp. [1]. However, *P. falciparum* infection is mainly responsible for most of the malaria-related morbidity and mortality, mostly among African children and pregnant women. WHO and other independent research organizations worldwide are continuously working to manage this lethal infection [2, 3]. There are two main strategies for the management and control of malaria infection. The first is to control the vector, and the second is to manage the infected cases [4, 5]. However, several agencies are also involved in the development of an effective vaccine. The most common vaccine, RTS, S has promising results. However, it has no effect on transmission, hence endemicity [6].

Management of infected cases basically relies on antimalarial drugs/combinations. However, the development of drug resistance and cross-resistance against most of the antimalarials (including atovaquone, sulfadoxine, pyrimethamine, and mefloquine, and even more recently the most efficacious artemisinin derivatives) and the declining efficacy of combinations in clinical practice is a big hurdle to case management [7, 8]. Therefore, there is an urgent need for the development of new therapeutic agents/drug combinations, which are effective in tackling drug resistance and have higher efficacy with faster action for the treatment of malaria, especially in developing countries. Antimalarial drug discovery can follow several strategies, ranging from minor modifications of existing agents to the design of novel agents that act against new targets. This article will discuss some common and important strategies for antimalarial drug discovery and the major associated challenges.

2. History of Drug Development for Malaria

Cinchona bark was the first effective antimalarial used in the seventeenth century, and its active ingredient, quinine, was isolated in 1820. Quinine became a treatment of reference for intermittent fever throughout the world, and it is still an important and effective treatment for malaria. The actual action mechanism of quinine remains controversial, but it is hypothesized that it acts on the asexual stage of the malaria parasite by inhibiting its heme polymerase enzyme, thereby inhibiting hemozoin formation, an essential process for the survival of the malaria parasite [9].

The first synthetic antimalarial drug, pamaquine, was developed in 1925 by German researchers by modifying methylene blue. Due to its low efficacy and high toxicity, pamaquine cannot be used for the treatment of malaria. But it provided lead compounds for the development of better antimalarial agents like mepacrine (quinacrine) [10].

Chloroquine (CQ) was first synthesized in Germany by Bayer Corporation in 1934 as a cheaper alternative to the costly naturally occurring quinine, but it was then considered toxic for any significant biological use [11]. However, in the late 1950s, a high level of resistance against CQ was reported from several parts of tropical and subtropical regions. The proposed action mechanism of CQ is the same as that of quinine [12].

Proguanil, a pyrimidine derivative and folate pathway inhibitor, was also introduced during World War II. Proguanil is currently being used as a fixed-dose combination with atovaquone for treatment and chemoprophylaxis agents for preventing malaria in travelers. It is an inhibitor of dihydrofolate reductase (DHFR) [13].

Atovaquone is a hydroxynaphthoquinone drug active against all *Plasmodium* species. Atovaquone acts by inhibiting parasite mitochondrial electron transport as it is an analogue of ubiquinone, a parasite mitochondrial electron carrier, which is the cofactor of dihydroorotate dehydrogenase [14]. The atovaquone-proguanil combination is well more effective than CQ alone, CQ-SP, or mefloquine (MQ) against multidrug-resistant *P. falciparum*. It is also effective in proguanil-resistant regions [15].

Pyrimethamine, which belongs to the same chemical class as proguanil, was further developed and is now being used as a fixed-dose combination with sulphadoxine (a sulfonamide and the structural analogues and competitive antagonists of p-aminobenzoic acid) for uncomplicated malaria since the late 60s. The sulphadoxine-pyrimethamine (SP) combination is commonly called Fansidar. Resistance to SP in Africa remained low until the late 1990s, but since then it has spread rapidly. The combination works by inhibiting two important enzymes of the folate pathway, dihydropteroate synthase (DHPS) and DHFR, respectively [16].

In the late 80s, MQ was developed as an effective treatment option for uncomplicated malaria through a collaborative project of the US Army Medical Research and Development Command, WHO/TDR, and Hoffman-La Roche, Inc [17]. MQ is an effective blood schizontocidal against all malaria species that infect humans, including the fifth species, *Plasmodium knowlesi*. Resistance to mefloquine was reported in Asia in 1985, around the time the drug became generally available. The exact mode of antimalarial action and biochemical basis of resistance to MQ are not known, but clinical resistance to MQ is associated primarily with the amplification of the pfMDR1 gene, which encodes a P-glycoprotein homologue1. MQ inhibits β-haematin formation, leading to a toxic accumulation of haem (ferriprotoporphyrin IX) in the parasite's food vacuole [18].

Another important antimalarial drug, piperaquine (PPQ), was synthesized by the Shanghai Research Institute of Pharmaceutical Industry in 1966 and was used as a replacement for CQ as the first-line monotherapy in China for malaria treatment [19]. The exact mechanism of action of PPQ is unknown. But it has been shown that it acts on the polymerization of haematin. The exact mechanism of resistance against PPQ is not well known yet; however, a copy number variation event on chromosome 5 of the malaria parasite was observed in PPQ resistance [20, 21].

Lumefantrine (LMF) was synthesized originally by the Academy of Military Medical Sciences in Beijing, China. The structure and mode of action are similar to those of QN and MQ. LMF is now recommended in combination with fast-acting artemisinin derivatives, such as artemether. In this combination, LMF is responsible for eliminating the residual parasites [22].

Pyronaridine, a benzonaphthyridine, was synthesized in China in 1970 [23]. The action mechanism of pyronaridine is similar to that of CQ [23]. Pyronaridine has been used extensively as monotherapy to treat *P. falciparum* and *P. vivax* infections by oral and parenteral routes in Hunan province. The action and resistance mechanism of pyronaridine are similar to those of CQ, but it has better antimalarial potential than CQ [24].

Artemisinin (ART) and its derivatives are derived/obtained from the plant *Artemisia annua*. *Artemisia annua*, an annual herb belonging to the *Asteraceae* family, has been used as an antimalarial herb in China for over 1000 years. *Artemisia annua*, also known as sweet wormwood, sweet annie, sweet sagewort, annual wormwood, or qinghao, is a common type of wormwood that is native to temperate Asia (mainly northern parts of China) but naturalized throughout the world. In 1971, the antimalarial activity of plant extract was experimentally proved in a primate model, and in 1972, ART was isolated and its chemical structure was described [24].

ART is an endoperoxide sesquiterpene lactone produced by the aerial parts (leaves) of *Artemisia annua* L. and is effective even against multidrug-resistant strains of the malaria parasite. Several derivatives of ART have been developed by semisynthetic substitutions to enhance the pharmacological profile of ART. ART and its derivatives are potent blood schizontocidal and gametocytocidal compounds that can cure infected patients and also act as transmission-blocking agents [24]. The presence of the endoperoxide bridge is the key factor and is responsible for the potent antimalarial potential of this class [25]. It is supposed that ART derivatives perform their action through the production of free radicals and reactive aldehydes [26].

ARTs perform their antimalarial action in two successive steps. The first step is the iron-mediated cleavage of the endoperoxide bridge, which generates an unstable organic free radical and/or other electrophilic species. The second step of alkylation involves the formation of covalent adducts between the drug and malarial proteins [26]. All the ART derivatives have specific physicochemical as well as biological properties. The main ART derivatives are artemether, arteether (AE), dihydroartemisinin (DHA), and artesunate (AS). Artemether (AM) is a methyl ether derivative of dihydroartemisinin, and it is synthesized by the reduction of dihydroartemisinin. AM can be given as an oil-based intramuscular injection or orally. It is also coformulated with LMF for combination therapy [27]. α/β arteether is an ethyl ether derivative of artemisinin. It is a potent, oil-soluble antimalarial. AE was developed by the CSIR-Central Drug Research Institute (CDRI), Lucknow, India, and consists of a mixture of α and β forms of AE in a 30 : 70 ratio. It was registered in India in January 1997 for use in malaria patients. This drug was marketed in India as an oil-based intramuscular injectable formulation [28]. Dihydroartemisinin (DHA) is the main active metabolite of the ART derivatives. It is relatively insoluble in water. Its antimalarial potential is similar to that of oral AS [29]. It can be given orally as well as by the rectal route. A fixed-dose formulation with PPQ [30]is currently being used as a promising new ART-based combination treatment (ACT). It is the most effective ART compound, has a strong blood schizonticidal action, and reduces malaria transmission. Artesunate (AS) is the sodium salt of the hemisuccinate ester of ART. It is soluble in water as well as in alkaline water but has poor stability in aqueous solutions at neutral or acidic pH. AS can be given orally, rectally, or by the intramuscular or intravenous routes [31]. A combination of MQ and AS is highly effective in treating multidrug-resistant malaria. Researchers are continuously working to find some new, potent, and safe antimalarial agents. Several new antimalarials and/or combinations are in different developmental stages and may be ready for use in the future for malaria patients (Table 1).

3. The Challenges with Antimalarials

Resistance to antimalarial drugs hampers control efforts and increases the risk of morbidity and mortality from malaria. Antimalarial drug resistance has been defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the tolerance of the subject [32]. In general, drug resistance appears to occur through spontaneous mutations in the target genes of the malaria parasite and is thought to be independent of the drug used. It may be a single mutation or multiple mutations. These genetic mutations in the genes responsible for producing the proteins related to the drug's parasite target or influx/efflux pumps lead to a reduction of intraparasitic concentrations of the drug. For example, mutations in the genes encoding the transporters PfCRT and PfMDR1 are responsible for CQ drug resistance and cross resistance to closely related drugs. However, the role of mutations in PfMDR1 in determining the therapeutic response following chloroquine treatment remains unclear. There are several other examples, like single-point mutations in the gene encoding cytochrome b (cytB), which confer atovaquone resistance, or in the gene encoding dihydrofolate reductase (dhfr), responsible for pyrimethamine resistance [33]. Immunity also plays a major role in the emergence and spread of drug resistance. Even a previously nonimmune individual develops a specific immune response to a malaria infection, and eventually the malaria parasite evades this response by programming antigenic variation in its main red cell surface-expressed epitopes. For example, *P. falciparum* infects erythrocyte membrane protein 1 (PfEMP1), which is encoded by the var multigene family and changes in 2-3% of parasites each asexual cycle. Drug resistance also depends on transmission in geographical areas, immunity, parasite load, and the PK-PD properties of the drug. Drugs with long half-lives, for which resistance is conferred by single-point mutations, select resistant parasites rapidly. Uncontrolled use and poor-quality or fake drugs also contribute to the emergence of resistance [32–35].

4. Important Strategies for Antimalarial Drug Discovery

4.1. Developing Analogues of Existing Drugs. During the last two decades, only a few chemical series have been identified and are in clinical practice as a new class of antimalarial drugs, including aminoalcohols (mefloquine, halofantrine, and lumefantrine), sesquiterpene trioxanes (artemisinin derivatives), and naphthoquinones (atovaquone) [13, 36, 37]. Identification and lead optimization of a new chemical series as potent antimalarial have several financial, social, and scientific hurdles. These challenges include toxicity, cost, and ethical issues [38–40]. On the other hand, the development of analogues of existing antimalarial drugs is an important and easy way to design new chemotherapeutic interventions, which can tackle the above problems to a greater extent [10, 41]. The development of trioxanes and analogues of 4-aminoquinolines are the best examples of this category [42]. Chloroquine (CQ) analogues synthesized by linking 4,7-dichloroquinoline with monoalkynes, ferroquine, a methalocenic CQ analogue, and 1,2,4-trioxane, which has a similar nucleus to artemisinin, are in clinical trials for the treatment of uncomplicated malaria [43–45].

4.2. Analysis of Compounds from Natural Products. Natural products have been used as traditional medicine for thousands of years and have contributed to the arsenal of modern medicine [46–52]. Most of the important and efficacious antimalarial drugs like atovaquone, artemisinin (and its semisynthetic derivatives), clindamycin (a derivative of the natural product lincomycin), erythromycin, and tetracycline have been identified from natural resources only [53–55].

There are several hurdles to overcome to develop antimalarial drugs from natural products, including moderate

Table 1: Important antimalarial drugs and their developmental stages.

Antimalarial	Year of development	Developmental phase
Quinine	1820	In clinical use
Chloroquine	1934	In clinical use
Proguanil	1945	In clinical use
Pyrimethamine	1952	In clinical use
Piperaquine	1966	In clinical use
Lumefantrine	1967	In clinical use
Pyronaridine	1967	In clinical use
Mefloquine	1974	In clinical use
Sulphadoxine	1981	In clinical use
Artemisinin	1972	In clinical use
Atovaquone	1991	In clinical use
Artefenomel	Under development	Phase 1
DSM265	Under development	Phase 1
M5717	Under development	Phase 1
Meplazumab	Under development	Phase 1
MMV688533	Under development	Phase 1
SAR441121	Under development	Phase 1
ZY-19489	Under development	Phase 1
Cipargamin	Under development	Phase 2
DM1157	Under development	Phase 2
MMV390048	Under development	Phase 2
SJ733	Under development	Phase 2
Tafenoquine	Under development	Phase 2
5-ALA HCl with SFC	Under development	Phase 2
Artefenomel-ferroquine	Under development	Phase 2
Imatinib-DHA-piperaquine	Under development	Phase 2
Methylene blue with artemether and lumefantrine	Under development	Phase 2
Ganaplacide with LUM-SDF	Under development	Phase 3
Artemether-lumefantrine	Under development	Phase 4

activity, toxicity, and characterization of physicochemical and biological properties, and most of the time, the isolation of a single drug candidate from the crude will lose the antimalarial potential. However, continuous research is going on worldwide for antimalarial drug development from natural products, and some of them are in clinical trials as well. The development of *Argemone mexicana* as a potent antimalarial is the best recent example of this [56, 57].

4.3. Drug Repurposing. Drug repurposing is an emerging trend to develop new chemotherapeutic interventions for many life-threatening diseases like malaria, cancer, tuberculosis, and diabetes [58–65]. It is safe, economic, and less time-consuming to reach the clinical stage as they are already approved for human use, and most of the clinical, pharmacological, pharmacokinetics, and pharmacodynamics information is available.

Several successful efforts have been done in this field, and various molecules have been identified with this approach, particularly for malaria treatment. Itraconazole (an antifungal agent) [66], atorvastatin (widely used to reduce cholesterol levels) [67], lopinavir and tipranavir (HIV protease inhibitors) [68], and the antifungal and antihelminthic compound imidazolopiperazine [68] are the best examples in this context. These molecules have been found to have potent antimalarial activity at different stages and against specific targets of the malaria parasite.

Moreover, several antibiotics like doxycycline, azithromycin, clindamycin, tetracycline, and fosmidomycin are in clinical use as combination partners for malaria treatment. One of the most important antimicrobial agents, sulfadoxine, has the most synergistic antimalarial effects when combined with pyrimethamine. Several countries have adopted this combination in their antimalarial policies [69–71].

4.4. Identification of New Drug Targets and Synthesis of Their Selective Inhibitors. Identification of new drug targets for antimalarial drug discovery is a major challenge in the context of multidrug-resistant malaria. Development of drug resistance against one particular antimalarial also reduces the efficacy of closely related drugs called "cross resistance," which reduces the options for case management to a greater extent [8, 35, 72, 73]. It is therefore necessary to identify some new vital targets and develop new pharmacophores against these targets [74–76].

Whole-genome sequencing of the malaria parasite opened new avenues for the identification of a new drug target [77]. Several key pathways and specific targets like type II fatty acid synthesis (FASII) [78], apicoplast and its various pathways [79–81], shikimate pathway [82], enzymes of the folate pathway [83], and many more from different vital pathways of the malaria parasite are being explored to identify a safe, vital target and its validation, as well as to

develop some new and safe therapies against these identified targets [84, 85].

High-throughput in vitro or virtual screening of chemical libraries from different resources is an emerging tool for identification and lead optimization [86]. This approach is not only valuable to develop a new antimalarial drug or combination but also its unique action mechanism will be beneficial to reduce/delay the chances of drug resistance either with existing antimalarial or with newly developed other candidates [87].

4.5. Identification of Resistance-Reversal Agents. Antimalarial drug resistance is emerging at a faster rate due to several reasons, like drug abuse, mutations in transporter genes, and mutations in identified target genes. Drug discovery is a time-consuming process that is primarily limited by the duration of lead optimization and clinical trials, their high cost, and strict regulatory rules. Therefore, it is important to optimize the existing antimalarials with proper strategies to reintroduce them into the mainstream.

However, the identification of resistance reversal agents is also a challenging task limited by a lack of action mechanisms and toxicity. Several resistance reversal agents have been identified for most of the traditional drugs like CQ (verapamil, chlorpromazine, promethazine, chlorpheniramine, and citalopram) [88–90], mefloquine, quinine, and quinidine (NP30) [91, 92].

Drug metabolizing enzymes also play an important role in declining efficacy and drug resistance. The excessive metabolism of traditional drugs like mefloquine, quinine, and quinidine may lead to reduced bioavailability, thereby declining the efficacy and inducing the chances of drug resistance. Inhibition of these drug metabolizing enzymes by specific inhibitors can reverse the situation, and the drug might remain effective. However, toxicity might be a major concern for these combinations and should be taken into consideration [93, 94]. Successful research has been done employing this resistance reversal approach. With the resistance reversal action of ketoconazole for mefloquine [95], the combination of clarithromycin with mefloquine/quinine/quinidine against multidrug-resistant malaria [93, 96] has been proved to be beneficial against MDR malaria.

4.6. Combination Therapy. Due to the emergence of drug resistance towards most of the antimalarial drugs, WHO banned monotherapy for malaria to reduce the chances of drug resistance. The rationale behind the combination is that if two drugs are used with different modes of action and therefore different resistance mechanisms, then the probability of developing resistance to both drugs at the same cell division is the product of their individual probabilities [97, 98].

Combination therapy with antimalarial drugs is the simultaneous or combined use of two or more blood schizontocidal drugs with independent modes of action. The different biochemical targets enable the combinations to improve therapeutic efficacy as well as delay the development of resistance to the individual components [33, 99–101].

Artemisinin-based combinations (ACTs) are recommended as first-line treatments for uncomplicated falciparum malaria worldwide. These derivatives are fast-acting and active against different stages of the malaria parasite. It is recommended that the other ACT partner drug have a longer half-life due to the shorter half-life of the artemisinin derivatives. The artemisinin derivatives are eliminated rapidly, and the partner drugs are eliminated slowly; therefore, there is complete protection for the artemisinin derivatives [99, 101].

Moreover, resistance/delayed parasite clearance against widely used antimalarial combinations, including ACTs, deteriorates the problem and poses a major threat to the development of new therapies [102–105].

4.7. Omics-Based Strategy. Multiomics technologies such as genomics, proteomics, and metabolomics have been widely used in recent years to provide a more holistic perspective of biological mechanisms, functional principles, and dynamics [106]. Omics approaches incorporating high-throughput technology, automation, and data mining have aided in a faster, more reliable, and economical understanding of the molecular pathways and critical proteins required in the parasite's life cycle, and hence the pathogenesis of this disease [107]. The transition to cell-based phenotypic screening has been a significant advancement in antimalarial drug discovery, with noteworthy improvements in the screening of compounds against the asexual blood stage, liver stage, and gametocytes. In vitro development of compound-resistant parasites followed by whole-genome scanning is a common strategy for therapeutic target deconvolution in *Plasmodium falciparum* [107]. This approach has been used to identify or confirm several of the most promising antimalarial drug targets, including translation elongation factor 2 (eEF2) and phenylalanine tRNA synthetase (PheRS). One disadvantage of this strategy is that if a mutant gene is uncharacterized, it may take a lot of time and effort to figure out whether it is a drug target, a drug resistance gene, or just a background mutation. As a result, having high-throughput, functional genomic datasets available can considerably aid target deconvolution. *P. falciparum* genome-wide essentiality mapping and transcriptional analysis of the host and parasite during *P. berghei* liver-stage infection have discovered potentially druggable pathways. The discovery of essential pathways involved in parasite development has been aided by advances in deciphering the epigenomic regulation of the malaria parasite genome. Furthermore, studying the host genome during infection has led to the discovery of new gene candidates linked to severe malaria susceptibility. One of the most successful omics-based approaches for discovering or rediscovering numerous specific novel targets of promising small compounds has been the forward genetics IVIEWGA (in vitro evolution and whole-genome analysis) method [108, 109].

4.8. Immunotherapy. Immunotherapy is an emerging and successful strategy to fight against several diseases, including malaria and cancer [110]. Checkpoint blockade immunotherapy is the most notable immunotherapy of recent times,

in which monoclonal antibodies (mAbs) are used to break the interaction between immune inhibitory receptor-ligand pairs [110]. This blocking leads to the facilitation of normal immune system function, thereby permitting enhanced immune responses against upregulated ligands. Cytotoxic T-lymphocyte-associated protein 4 (CTLA4), death 1 ligand 1 (PD-L1), T-cell immunoglobulin, mucin domain-containing protein 3 (TIM3), OX40, GITR, and CD69 are the main targets for these mAbs [110].

Recently, one independent preclinical study showed that a multimeric form of PD-L2 fused with the Fc part of immunoglobulin (PD-L2-Fc) was sufficient to reduce the lethal malaria infection and mediate survival following re-infections after several months without additional PD-L2-Fc [111]. Combined inhibition of PD-L1 and LAG3 by mAbs increases the clearance of malaria parasites, facilitates CD4+ T cell function, and increases antibody titres [112]. It has also been shown that inhibition of OX40 signaling also increases helper CD4+ T cells and humoral immunity, thereby increasing parasite clearance during nonlethal malarial infections [113]. Preclinical studies have also shown that inhibition of CTLA4 or PD-L1 increases T cell activation and increases the incidence of cerebral malaria [114].

5. Conclusions and Future Directions

Although a marked reduction in malaria incidence and mortality has been reported in recent years due to the introduction of ACTs in antimalarial policy, the development of drug resistance against most of the antimalarials, especially artemisinin derivatives, is an alarming situation. The introduction of new drugs/combinations in the antimalarial arsenal is an immediate need. Based on resources, one or more of the strategies discussed above should be explored for the development of new chemotherapeutic interventions for malaria. Importantly, the use of genomics and omics-based methodologies has resulted in significant breakthroughs in the identification of novel targets in protozoan diseases.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Disclosure

Swaroop Kumar Pandey Current Affiliation: Department of Biotechnology, GLA-University, Mathura, India-281406. Email: swaroop.pandey@gla.ac.in.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Swaroop Kumar Pandey and Uttpal Anand contributed equally to this work. All the authors of this manuscript have substantially contributed to the concept, literature mining, writing of the manuscript, provided critical feedback and revised the manuscript critically. All authors contributed to the writing or revision of the final manuscript.

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