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Antimalarial Drug Discovery: From Quinine to the Dream of Eradication

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ABSTRACT: The search for antimalarial remedies predates modern medicine and the concept of small molecule chemotherapy, yet has played a central role in the development of both. This history is reviewed in the context of the current renaissance in antimalarial drug discovery, which is seeing modern drug discovery approaches applied to the problem for the first time. Great strides have been made in the past decade, but further innovations from the drug discovery community will be required if the ultimate dream of eradication is to be achieved.

Malarial disease has caused greater suffering and mortality over the course of human history than perhaps any other single malady. Even today, a third of the world's population lives under the threat of infection and hundreds of millions suffer the acute effects of disease every year. Malaria still claims more than 600,000 lives every year, mostly young children who have not yet established protective immunity. The search for antimalarial remedies predates by millennia a scientific understanding of the disease, and the active components of current artemisinin combination therapy claim chemical provenance with the earliest herbal remedies for (malarial) fevers. The history of antimalarial drug discovery is a rich one that contributed fundamentally to the modern concept of chemotherapy and played no small role in the emergence of the pharmaceutical industry itself in the last century. What lessons, if any, does this past history hold for us as drug discovery scientists today? How have academic laboratories, the pharmaceutical industry, and public and private funders collaborated to produce what is currently a burgeoning pipeline of new antimalarial drug candidates? Can these successes be leveraged in future mass drug administration campaigns to eliminate disease in endemic areas, or even eradicate malaria globally? These are important questions that will ultimately be answered by scientists and clinicians who recognize both a moral imperative and a complex and challenging problem worthy of engagement on purely scientific grounds.

Of the species of *Plasmodium* parasites that infect humans, *P. falciparum* and *P. vivax* are responsible for the greatest disease burden. Malaria is transmitted by the female anopheline mosquito, which on taking a blood meal deposits perhaps a dozen malaria sporozoites. The sporozoite must transit numerous physical and biological barriers en route to the liver where, upon infecting a hepatocyte, a single sporozoite spawns tens of thousands of merozoites. The merozoites are expert invaders of erythrocytes and propagate a cycle of infection that is responsible for symptomatic, blood-stage disease. The process of disease transmission begins with the differentiation of blood-stage parasites into gametocytes that can then be taken up by the mosquito vector. Most insidiously, *P. vivax* and *P. ovale* parasites can form liver-stage hypnozoites that lie dormant for extended periods, only to re-emerge long after therapy has ceased. The complexity of the parasite life-cycle (much simplified here) and its various interactions with the human host and mosquito vector suggests a multitude of potential drug targets for intervening in disease and/or transmission. So what did the earliest drug hunters find in their empirical search for naturally occurring remedies? This history[1,2] is well worth reviewing, not least because two of the natural products identified (quinine and artemisinin, Figure 1) helped to reveal an Achilles' heel of the parasite that continues to be exploited therapeutically today.

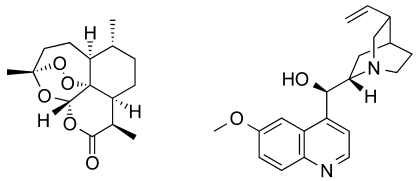

Figure 1. Prototypical antimalarial agents artemisinin and quinine.

The bark of the cinchona tree native to South America provides a rich source of medicinal alkaloids. The first use of the bark in treating malaria is often attributed to Jesuit missionaries in 17th century Peru, though the indigenous population used hot infusions of the bark much earlier to combat shivering in cold and damp conditions.[1] Whatever its actual provenance, the discovery of 'Jesuit's Bark' caused a sensation in Europe and its use was rapidly adopted. Quinine was first isolated from cinchona bark in France in 1820, and the superiority of the pure alkaloid as compared to the bark was quickly appreciated. With pure quinine in hand, the appropriate dosage could be reliably established, and so was born the first chemotherapeutic, in the modern sense of the word. Although the structure of quinine would not be established until the early 20th century, an ambitious attempt at its synthesis in 1856 led serendipitously to the discovery of the first aniline dye, mauveine. This discovery launched a synthetic dye industry

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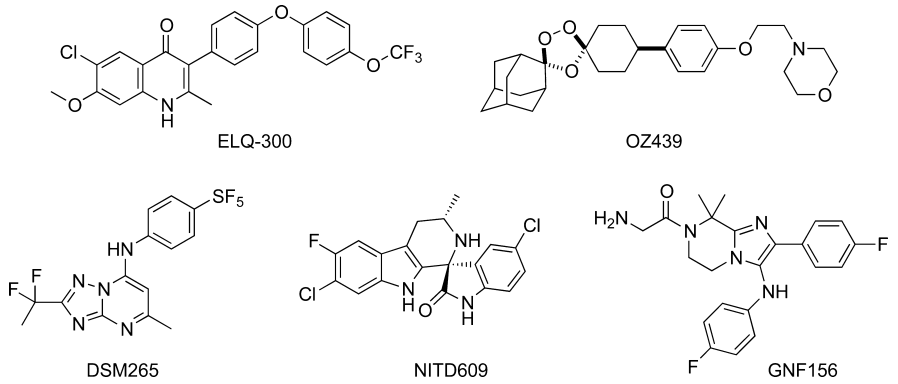

Figure 2. Preclinical and early stage clinical drug candidates.

that would in turn enable Paul Ehrlich's seminal work establishing the concepts of small molecule pharmacology and selective toxicity of chemotherapeutics. The pharmaceutical industry that soon emerged would produce among its early products synthetic antimalarials like chloroquine and quinacrine that would come to supplant the use of quinine.

In China, the use of sweet wormwood (*Artemisia annua*) in treating fevers dates back at least two millennia. In the late 1960s, in support of the North Vietnamese army, the Chinese government launched a research program to identify active antimalarial agents from traditional Chinese herbal medicine.[2] By the mid-1970s, Chinese scientists had succeeded in isolating and structurally characterizing artemisinin (qinghaosu), a sesquiterpene endoperoxide with a structure so remarkable that the work received a skeptical reception when it first appeared in the west. The antimalarial properties of the compound were undeniable, however, and the development of semisynthetic analogues suitable for oral dosing soon followed. Today artemisinin combination therapy (ACT) constitutes the standard of care in treating uncomplicated *falciparum* malaria. Typically, the rapid action of the artemisinin component is combined with an agent exhibiting a more sustained antimalarial effect (often a synthetic quinoline). Thus, the exploits of the earliest drug hunters continue to pay dividends today via the chemical progeny of quinine and artemisinin.

The clinical success of ACT has sparked renewed interest in understanding how the artemisinins and quinolines exert their parasite killing effects. Interestingly, both compounds appear to target the hemoglobin degradation pathway by which the parasite obtains amino acids during blood-stage infection. Specifically, it is the unbound ferrous iron heme produced during hemoglobin catabolism that is hypothesized to activate artemisinins via reduction of the endoperoxide bond. The downstream consequences of this reaction are still debated, but the importance of the initial reduction is widely accepted. Quinolines, however, are thought to interfere with the parasite's heme detoxification pathway, a remarkable process in which heme dimers are assembled into an inert biocrystalline material called hemozoin. The targets of these drugs are therefore not genomic but are instead unique chemical and supramolecular processes that emerge only via interactions of the parasite with host erythrocytes. Accordingly, it appears unlikely that the artemisinins or quinolines would be rediscovered using a reductionist, target-based approach to drug discovery. This observation raises the question of how best to approach antimalarial discovery with current tools and technologies.

As it happens, the past decade has seen a renaissance in antimalarial drug discovery, made possible in part by the vision and munificence of organizations like the Wellcome Trust and the Bill and Melinda Gates Foundation. This period also marks the first time target-based approaches have been applied to antimalarial discovery. While there is no shortage of genomically validated antimalarial drug targets, there is most certainly a shortage of chemistry resources necessary to produce appropriately selective and potent small molecules to test therapeutic hypotheses. Fostering and funding collaborations between academic laboratories and industrial partners offers one possible solution to this problem. An early example of such collaboration involved the efforts of UCSF and GSK scientists to target falcipains, parasite cysteine proteases involved in hemoglobin degradation. This collaboration succeeded in producing potent, efficacious molecules and reached the stage of candidate selection.[3] There have been other successes of target-based approaches, but the more recent trend is unmistakably in the direction of whole-cell screening, where the full biological complexity of the parasite and its interaction with the host cell can be interrogated.

So, what's in the pipeline currently? A Global Malaria Portfolio is published quarterly by Medicines for Malaria Venture (http://www.mmv.org/research-development/rd-portfolio). Among products in late-stage clinical trials are pediatric formulations of ACT, other nonartemisinin combinations, and the 8-aminoquinoline tafenoquine, which is effective against persistent liver-stage hypnozoites. The early stage clinical pipeline includes new quinolines and artemisinins as well as entirely new classes of agents (Figure 2). Among compounds identified using target-based approaches is the compound DSM-265,[4] an inhibitor of *P. falciparum* dihydroorotate. The reexamination of orphaned leads is a pragmatic approach, and in this vein, the discovery of ELQ-300[5] resulted from in vivo optimization of the avian antimalarial endochin. The clinical success of artemisinins has inspired the exploration of a wide variety of synthetic peroxides as antimalarials. The 1,2,4-trioxolane arterolane was this first synthetic peroxide to enter human clinical trials and is now being followed by a second analogue (OZ439)[6] with improved in vivo properties. As noted above, screening in whole-cell proliferation assays has proved successful in the search for novel mechanisms and chemical matter. Current investigational compounds that emerged from this approach include the spiroindolone NITD609[7] and the imidazolopiperazine GNF156.[8] Far from a comprehensive list, the examples provided here provide an

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indication of the diversity of approaches being explored and the equal diversity of chemical matter that has resulted.

Looking at the current preclinical and clinical pipeline, one can be optimistic about the future of antimalarial chemotherapy. Buoyed by these successes, the field is looking ahead to future challenges such as blocking disease transmission, eliminating disease in specific geographic areas, and eventually eradicating the disease globally. This will be an epic undertaking requiring coordinated efforts in vector control, vaccination, and in the distribution and administration of chemotherapy and prophylaxis. Compounds designed to block transmission by acting on insect-stage parasites could also play an important role. Historically, mass drug administration (MDA) campaigns have succeeded in dramatically reducing transmission rates in specific geographic areas. While MDA is receiving renewed interest, there are certain inherent risks with this approach. First, drugs used in MDA should be exceptionally safe, given that asymptomatic and uninfected individuals will be treated with drug. To block transmission, the agents must be effective against gametocytes and especially the dormant liver-stages of *P. vivax* and *P. ovale*. Currently, the 8-aminoquinolines primaquine and tafenoquine (phase 3) are the only agents that possess this profile of activity. Unfortunately, both compounds present safety risks to patients with glucose-6-phosophate dehydrogenase deficiency and so their use in MDA may be limited to settings where safety monitoring and G6PD testing is possible.

Overall, it is clear that current tools and approaches are insufficient for the large-scale MDA efforts that will likely be required.[9] Perhaps some of the new compounds currently in the clinical will figure in future elimination and eradication efforts. Time will tell, but more than likely it will be necessary to develop new agents and new forms of existing agents intended specifically for MDA. Without a doubt there will be huge scientific, logistical, political, and economic hurdles to overcome in achieving the dream of eradication. Those currently engaged in the effort may not see the goal achieved in their lifetimes. Still, the successful elimination of this ancient scourge would certainly rate among the foremost achievements of medicine. Is the drug discovery community up to the challenge?

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Notes

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