Developing Long-Term Malarial Chemoprophylactic Compound Releasing Implants

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ABSTRACT

Despite the successful development of chemoprophylactic compounds and multi-drug combination therapies, malaria infection remains a crucial health threat to U.S. Soldiers in malaria endemic areas. The successful prevention of malaria infection is highly dependent on compliance with a prescribed chemoprophylaxis regimen. The Experimental Therapeutics (ET) Branch at Walter Reed Army Institute of Research (WRAIR) is the U.S. Army's premier research program for the development of anti-malarial prophylaxis drugs. A current effort of ET, in scientific collaboration with the Southwest Research Institute and Titan Pharmaceuticals, is to develop long-term release implantable anti-malarial drug matrices. These implants provide continuous drug release with a non-fluctuating drug levels over an extended period from two to six months, and could potentially relieve deployed service members from adherence to a daily oral drug dosing schedule. EVA (ethylene-vinyl acetate) implants that contain piperaquine, an compound effective against blood stage parasites, was tested in a mouse model with *Plasmodium berghei* to characterize the pharmacokinetics (PK) profile and long-term prophylactic efficacy *in vivo*. The piperaquine formulated implant study showed the PK profile exhibited slow drug release for six weeks while maintaining stable plasma levels. Furthermore, the piperaquine implants after longer than eight weeks of implantation demonstrated sufficient suppression in early blood stage malaria and complete protection from infection of *Plasmodium berghei* parasites in mice. The development of long-acting prophylactic implants with greater potency and safety is a novel approach, and one that could greatly improve compliance of deployed service members in malaria endemic regions. Furthermore, the target products will support the multi-domain battlefield operational concept by allowing ground combat forces maneuver and perform in an uninterrupted manner in resource-constrained environments. These preliminary findings with piperaquine allow us to pursue a series of long-acting implants that include more regulatorily attractive FDA-approved anti-malarial drugs, atovaquone/proguanil (Malarone®) and doxycycline, for follow-on *in vivo* preclinical studies.

BACKGROUND

1. The US Army Medical Research and Materiel Command (USAMRMC)'s mission is to ensure US forces are in optimal health and equipped to protect themselves from disease and injury. USAMRMC's products are developed via progression through the Medical Product Development Lifecycle (Fig. 1).

2. ET at WRAIR has adapted the overall USAMRMC product life cycle for small molecule drug development (Fig. 2), and utilizes a pharmaceutical industry-type, gated and tiered testing paradigm (Fig. 3) to develop candidate products for malaria, leishmaniasis, and antibiotic-resistant bacteria.

3. Malaria is the largest DNBI (disease, non-battle injury) threat for deployed US troops in malaria endemic regions.

4. The 4 current FDA-approved malaria chemoprophylaxis regimens all have issues with resistance, safety/tolerability, and/or compliance.

5. Incorporating antimalarial drugs into the ProNeura matrix to increase the duration of prophylaxis is being evaluated by ET in collaboration with the Southwest Research Institute and Titan Pharmaceuticals.

6. ProNeura (Titan Pharmaceuticals) is a FDA-approved long-term drug delivery platform, and is an ethylene vinyl acetate (EVA) based matrix (Fig. 4). Its therapeutic application is proven from the use of buprenorphine blended ProNeura to treat opioid addiction [2].

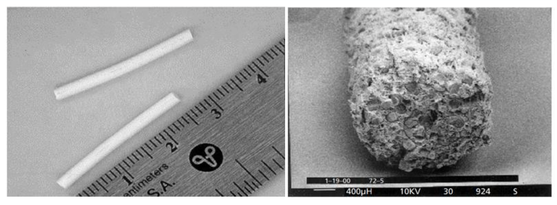


Figure 4. Ethylene vinyl acetate (EVA) implant [1].

Figure 1. USAMRMC Medical Product Development Lifecycle

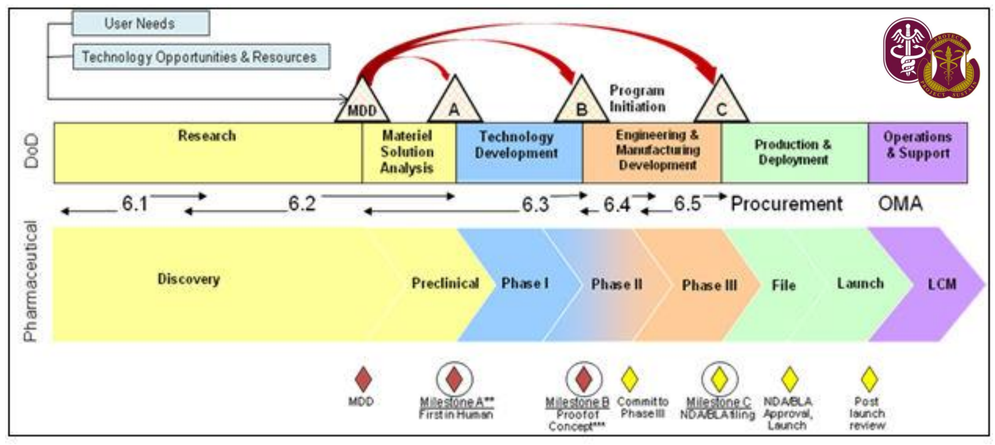
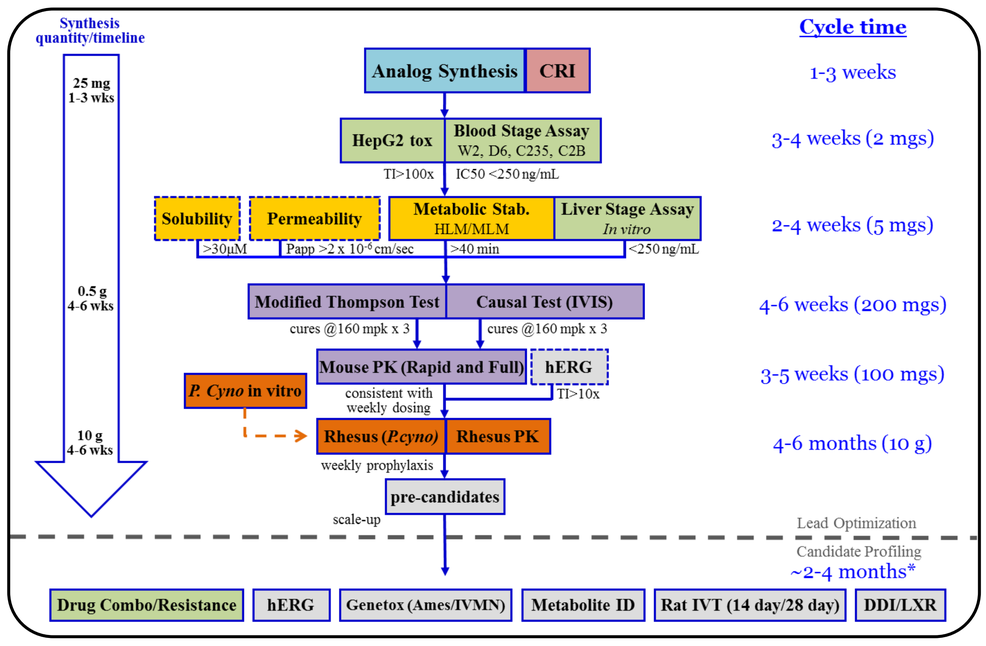


Figure 2. ET's Drug Discovery and Development Lifecycle

Figure 3. ET's Malaria Testing Strategy



RESULTS

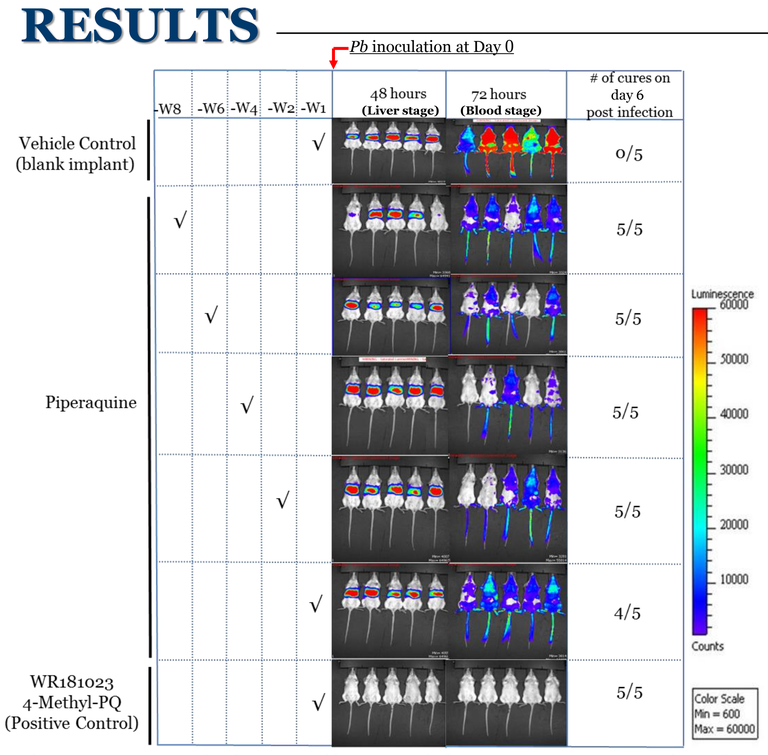


Figure 5. Prophylactic efficacy of the piperaquine-infused EVA (63.0 mg per implant) against blood stage malaria in mice infected with luciferase-transgenic *P. berghei*. *Pb* infection at day 0. W: weeks prior to *P. berghei* inoculation. Images acquired by IVIS (*in vivo* imaging system).

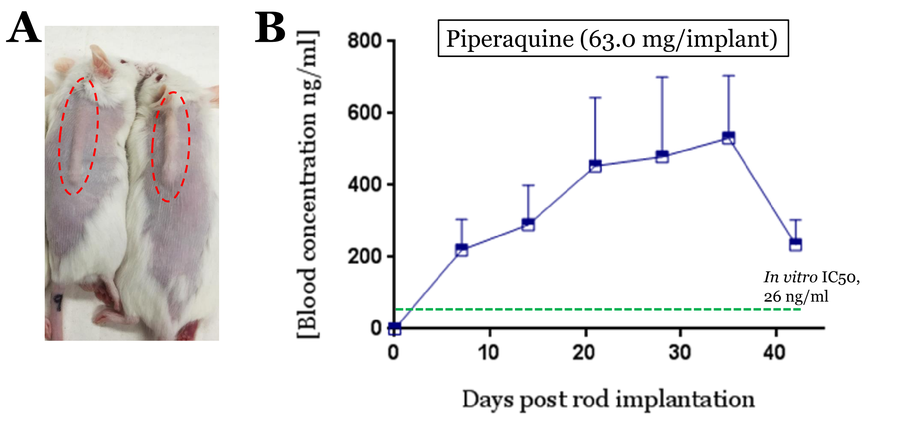


Figure 6. **(A)** Piperaquine-infused EVA implants (red dotted circles) are inserted into the back of mice. **(B)** Piperaquine blood concentration.

- The piperaquine-infused EVA implants release piperaquine gradually *in vivo* with the maximum blood concentration reached at week 5 (Fig. 6B).

- Piperaquine-infused implants protect mice from malaria infection up to 8 weeks post implantation (Fig. 5).

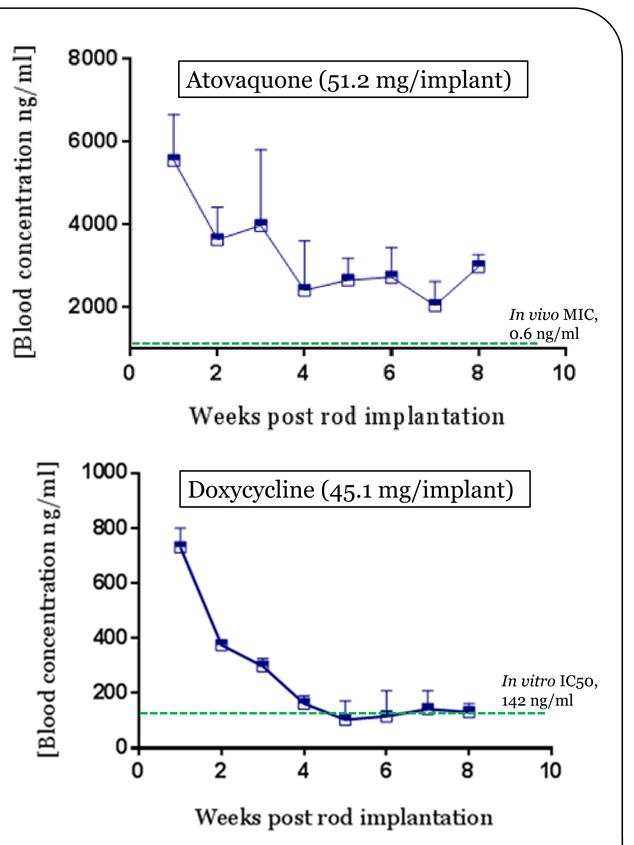


Figure 7. Atovaquone and Doxycycline blood concentration.

- Additional pharmacokinetic studies show the prolonged release of atovaquone and doxycycline from the EVA implants (Fig. 7).

- The goal is to develop the FDA-approved antimalarial drug-infused EVA implants including atovaquone/proguanil (Malarone®) and doxycycline.

CONCLUSIONS

1.Demand is high for a long-term prophylactic regimen for malaria prevention in resource-constrained environments, and an implantable sustained release formulation was a conceptual solution.
2.The challenge is to develop implants with sustained prophylactic efficacy for a minimum of 5 weeks, with good safety and tolerability.
3. Initial studies with the early blood-state drug piperaquine prove a preliminary "proof-of-concept" for the approach.
4. It is our goal to expand the preliminary findings to establish a series of antimalarial drug infused EVA implants, and that those will yield viable candidates for further development.

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