Developing Long-Term Malarial Chemoprophylactic Compound Releasing Implants

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ABSTRACT

Successful prevention of malaria is highly dependent on compliance with a prescribed daily chemoprophylaxis regimen. However, maintaining drug compliance by U.S. service members can be difficult due to a daily oral dosing requirement, side effects such as nausea and photosensitivity, organizational culture, command emphasis and the demands of the operational environment. 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 non-fluctuating drug levels over an extended period and could potentially relieve deployed service members from adherence to a daily oral drug dosing schedule. EVA (ethylene-vinyl acetate) implants containing atovaquone, a compound effective against liver- and blood-stage malaria parasites, were tested in a mouse model with *Plasmodium berghei* to characterize the pharmacokinetic (PK) profile and long-term prophylactic efficacy *in vivo*. The atovaquone-containing implant study showed the PK profile exhibited slow drug release for eight weeks while maintaining stable plasma levels. Furthermore, after twelve weeks of implantation, the atovaquone implants demonstrated complete protection from infection by *Plasmodium berghei* parasites in mice. The development of long-acting prophylactic implants with greater potency and safety is a novel approach that could greatly improve the 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 to maneuver and perform in an uninterrupted manner in resource-constrained environments. These preliminary findings with atovaquone and doxycycline allow us to pursue a series of long-acting implants that include the FDA-approved anti-malarial drugs, combination 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. ProNeura™ (Titan Pharmaceuticals) is a long-term drug delivery, subdermal implantable, ethylene vinyl acetate (EVA)-based matrix system (Fig. 4)[1]. Probuphine® (6 month, buprenorphine HCl implants), a ProNeura-based product, is the first product approved by the FDA for maintenance treatment of opioid addiction [2].

6. The incorporation of 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.

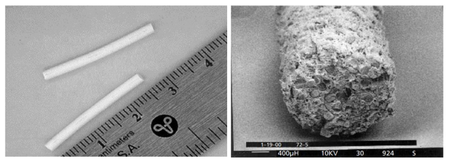


Figure 4. ProNeura™ (EVA-based) implant.

Figure 1. USAMRMC Medical Product Development Lifecycle

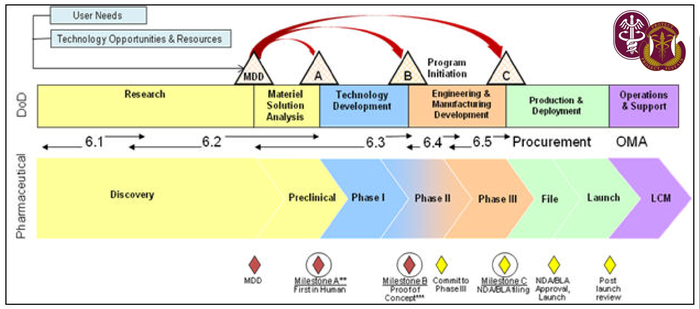
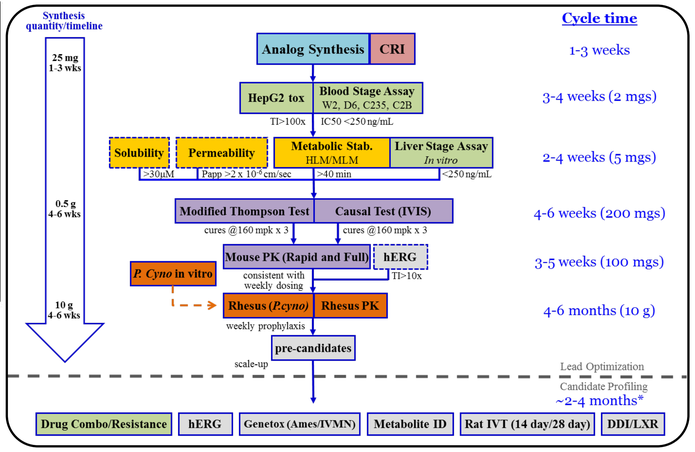


Figure 2. ET's Drug Discovery and Development Lifecycle

Figure 3. ET's Malaria Testing Strategy



RESULTS

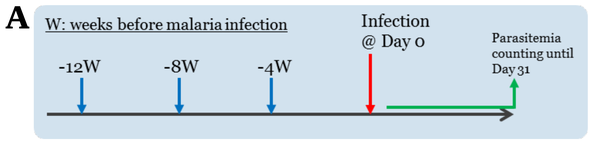


Figure 5. Prophylactic efficacy of the atovaquone-containing EVA implants against *P. berghei* malaria infection in mice. **(A)** Study design. **(B)** Different size s of atovaquone-containing rods were subdermally inserted into the back of mice. **(C)** Complete protection from malaria infection up to 12 weeks with atovaquone-containing implants.

C

Treatment		Prevention from malaria infection
Primaquine, oral admin		5/5
Blank implant		0/5
Atovaquone implants	4 weeks, whole	5/5
	8 weeks, whole	5/5
	8 weeks, 1/2	5/5
	8 weeks, 1/4	5/5
	8 weeks, 1/8	5/5
	12 weeks, whole	5/5

- The atovaquone-containing ProNeura™ implant demonstrates sustained release of atovaquone above the therapeutically relevant plasma level for up to 8 weeks (Fig. 6A).

- Atovaquone-containing implants protect mice from malaria infection for up to 12 weeks post-implantation (Fig. 5C).

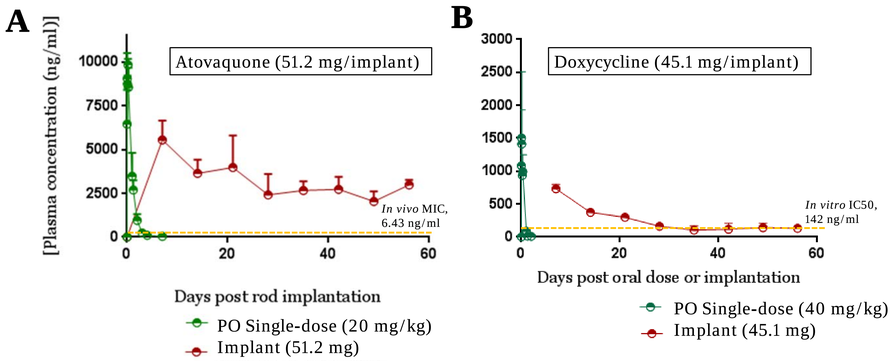


Figure 6. Atovaquone **(A)** and Doxycycline **(B)** blood concentration following implantation in mice.

- Additional pharmacokinetic study in mice shows the sustained release of doxycycline from ProNeura™-based implants (Fig. 6B).

- The goal is to develop ProNeura™-based EVA implants containing FDA-approved antimalarial drugs: atovaquone/proguanil (Malarone®) or doxycycline, for the increased long-term compliance of a prophylactic treatment for malaria prevention.

CONCLUSIONS

1.Demand is high for a long-term prophylactic treatment regimen for malaria prevention in resource-constrained environments, and an implantable, sustained-release formulation is a novel conceptual solution.
2.The challenge is to develop implants with sustained prophylactic efficacy for a minimum of 9-12 months, with good safety and tolerability.
3. Initial studies with atovaquone- and doxycycline-containing ProNeura™ implants prove a preliminary "proof-of-concept" for this approach.
4. Our goal to expand these preliminary findings to formulate a series of antimalarial drug-containing implants, based on Malarone® or doxycycline, and select viable candidates for further development.

REFERENCES

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[2] Rosenthal RN, Ling W, Casadonte P, Vocci F, Bailey GL, Kampman K, Patkar A, Chavoustie S, Blasey C, Sigmon S, Beebe KL. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction. 2013 Dec;108(12):2141-9.