Weill Cornell Medicine

Artemisinin-Proteasome Inhibitor Conjugates for the Treatment of Malaria

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Background & Unmet Need

- With over 200 M cases annually and 500 K deaths, mostly in children, malaria remains a persistent global health crisis
- *Plasmodium falciparum (Pf)* has developed resistance to all currently available antimalarials, including the artemisinins (ARTs), a key therapy
- ART is a pro-drug converted to radicals within the parasites, causing oxidative damage that overload the parasites' ubiquitin-proteasome degradation system (UPS)
- However, ART resistance is spreading in Southeast Asia and has also been reported in Africa •
- **Unmet Need:** Novel antimalarials as components of combination therapy to prevent further dissemination of ART resistance

Technology Overview

- **The Technology:** ART and Pf20S inhibitor hybrids (Artezomibs, ATZs) as dual mechanism therapies for the treatment of wild type and resistant Pf strains
- The inventors first demonstrated that conjugation of an ART moiety to a proteasome inhibitor did not interfere with the binding and inhibition of Pf20S
- The inventors then designed four new ATZs, in which the artesunate analog WZ-1840 is conjugated to a proteasome inhibitor via a propionate linker
- **PoC Data:** In growth inhibition assays of Pf Dd2 and two proteasome inhibitor-resistant strains, the ATZs substantially overcame resistance to the proteasome inhibitor moiety alone conferred by Pf20s point mutations
- The ATZs demonstrated ~5x improvement for Dd2 mutant β6A117D and ~100x improvement for Dd2 mutant β5A49S compared to the proteasome inhibitor WZ-1839 alone

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Patents:
PCT Application Filed
US Application Filed
EP Application Filed

Publications:
Zhan et al. *Cell Chem Biol.* 2023.

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Technology Applications

- Treatment and prevention of malaria infection
- Combination therapy to overcome ART resistance
- Strategy for the direct conjugation of other compound with anti-malarial activity

Technology Advantages

- Conjugate approach combines two MOAs in a single compound (artemisinins and proteasome inhibitors)
- Overcomes Pf treatment resistance to individual therapies
- Therapeutic activity of each moiety is preserved

Supporting Data / Figures

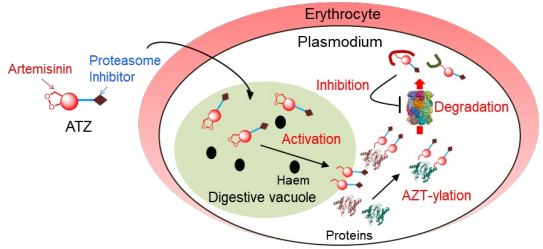

Figure 1: Conjugate artemisinin-proteasome inhibitors (ATZs) retain both proteasome inhibitory activity and the reactive alkylating activity of ART for synergistic inhibition of *Pf* parasites

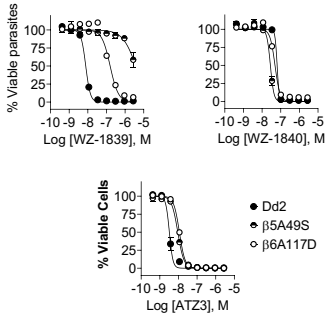

Figure 2: ATZ3 is more effective against *Pf* Dd2 and two proteasome inhibitor-resistant derivatives than the proteasome inhibitor WZ-1839 and the ART analog WZ-1840, suggesting the ATZ conjugate has a synergistic effect.

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