

Development of Trioxolane Drug Hybrids for the Targeted Delivery of Antimalarial Agents

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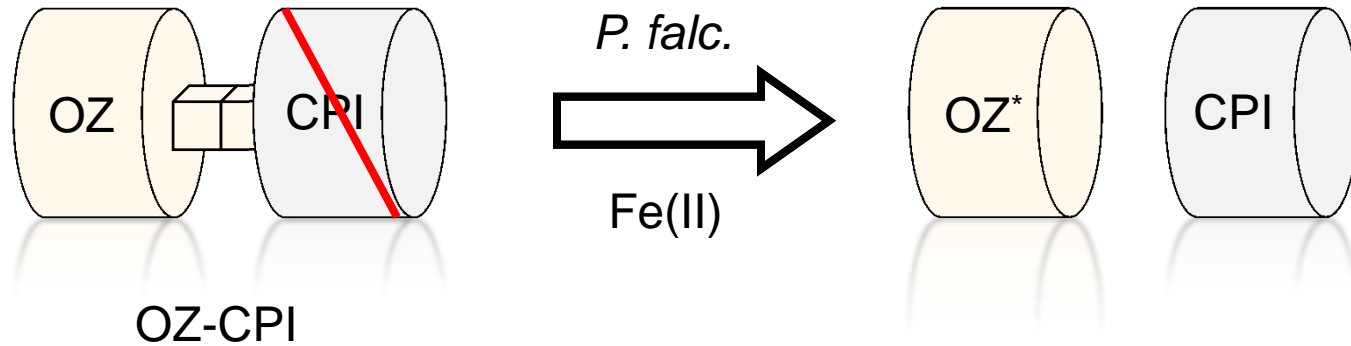
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Past and Current Funding

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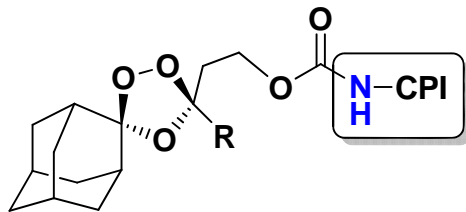
Concept: Iron(II) Dependent Drug Delivery



OZ-CPI

Inactive protease inhibitor (CPI)

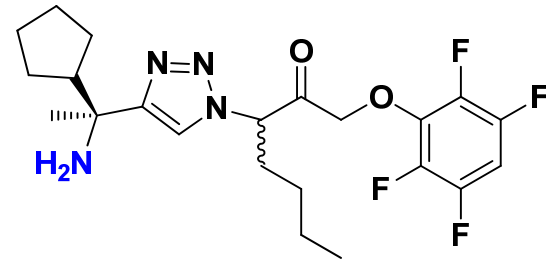
CPI activated only within parasite



OZ-CPI

- Trioxolane moiety from clinical-stage drug candidate OZ439
- 'traceless' linker to drug (CPI)

W2 *P. falc.* EC₅₀ ~4 nM

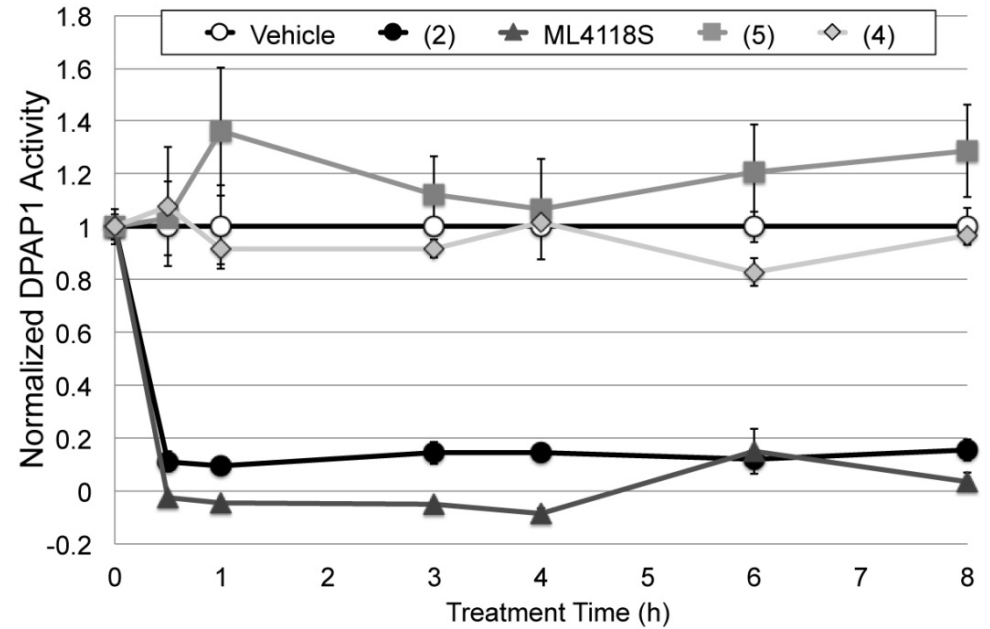
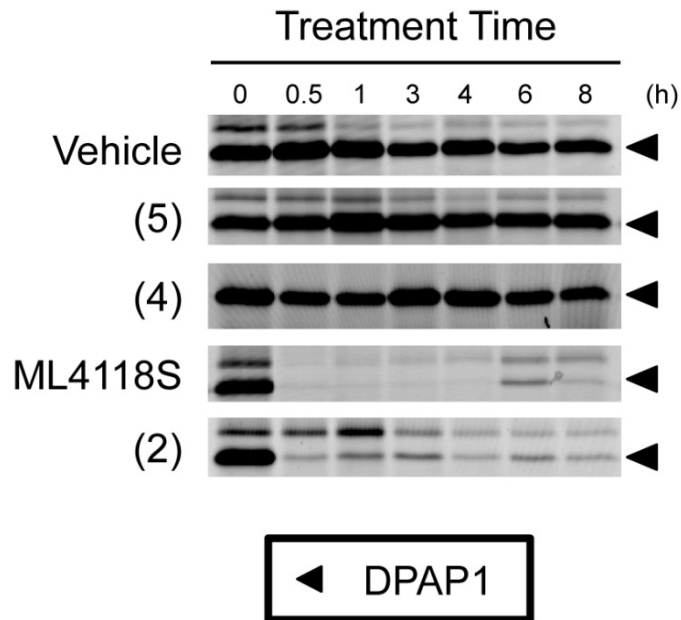
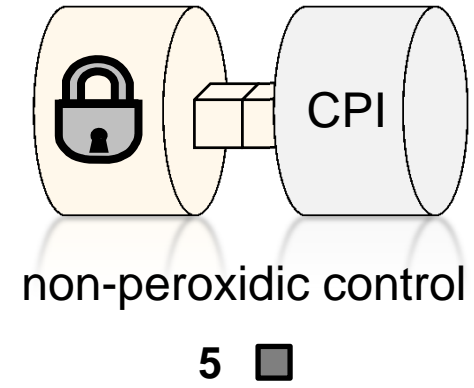
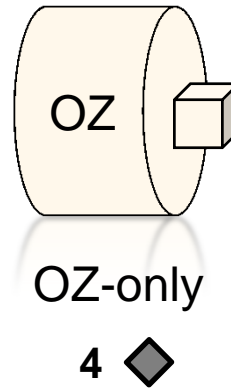
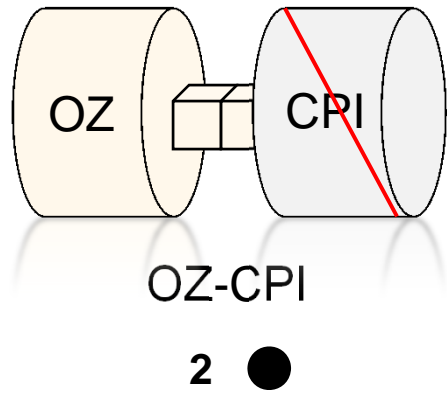


CPI (aka ML4118S)

- *irreversible* inhibitor of DPAP1
- also inhibits mammalian cathepsins
 - toxic in mice

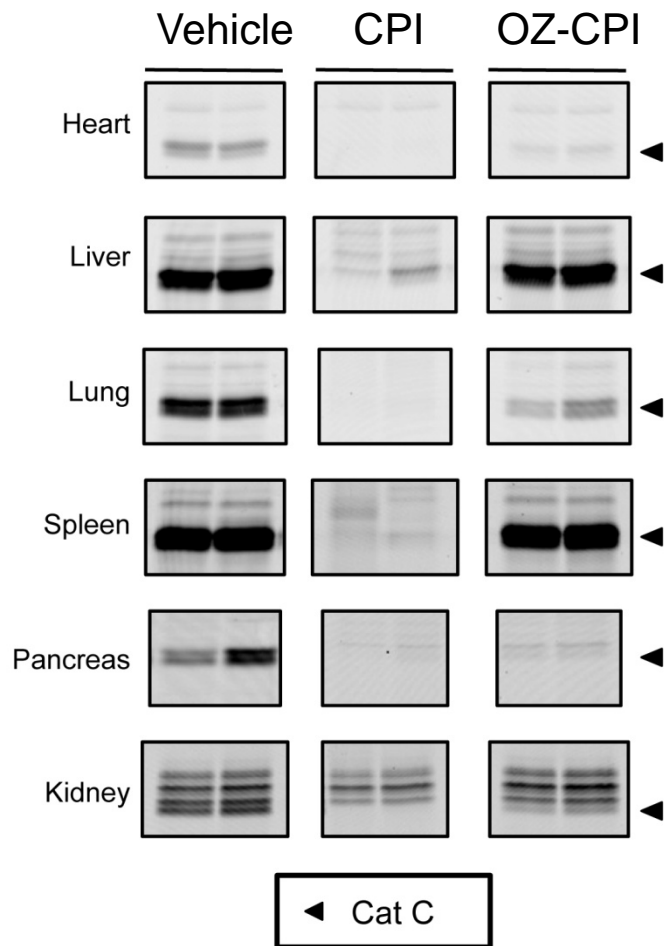
W2 *P. falc.* EC₅₀ ~5 nM

Inhibition of *PbDPAP1* in *P. berghei* Infected Mice

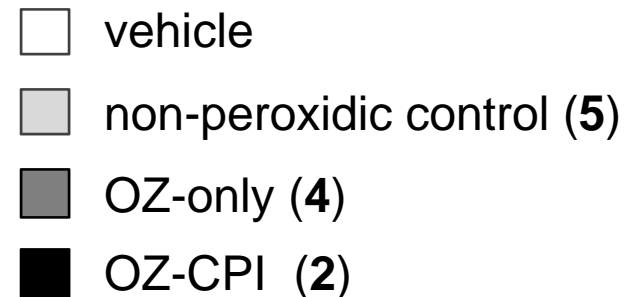
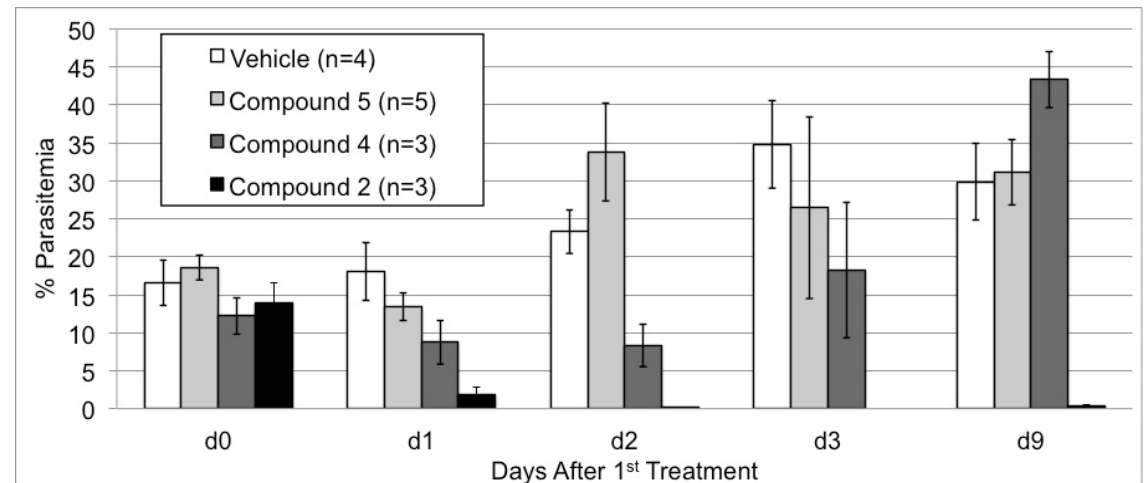


Benefits of Iron(II)-Dependent Delivery

Cat C inhibition in host tissue



Reduction in parasitemia



- Mouse cat B, S, and L were also inhibited in vivo by CPI but not by OZ-CPI
- Delivery of CPI in its iron(II)-targeted form is more selective *and* efficacious