



Department of Biochemistry and Molecular Biology

2017 Seminar Series – PhD Oration



**Wednesday 26th of July
12-1pm**

**Bio21 Institute Auditorium
30 Flemington Road, Parkville**

Jess Bridgford

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Molecular mechanisms of artemisinin action and resistance in the malaria parasite *Plasmodium falciparum*.

Artemisinin-based combination therapies are the standard treatment for *Plasmodium falciparum* malaria. Tu Youyou was awarded a Nobel Prize in Medicine in 2015 for her discovery of artemisinin, yet the mechanism of action of this life saving drug remains largely unknown. Here we show that the clinically relevant ART derivative dihydroartemisinin (DHA) inhibits the parasite proteasome, resulting in a build-up of polyubiquitinated proteins, unfolded (or misfolded) proteins and activation of the unfolded protein response. Disruption of this phenotype by co-treatment of parasites with DHA and chemical inhibitors of polyubiquitination prevents polyubiquitinated proteins from accumulating and dramatically rescues parasites from DHA-induced killing. These findings highlight accumulated polyubiquitinated proteins in themselves as toxic species that induce cell death, providing significant insight into our understanding of cellular proteostasis more broadly. We suggest a strategy of targeting the parasite ubiquitin-proteasome system with new antimalarials, such as proteasome inhibitors, which act synergistically with DHA, to fight the recent emergence of artemisinin-resistant infections.

*ALL WELCOME. Please join us for Pizza to celebrate this PhD Oration!
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