Department of Biochemistry and Molecular Biology

2018 Seminar Series

Wednesday 18th of April
12-1pm
Bio21 Institute Auditorium
30 Flemington Road, Parkville

Dr Stanley Xie

Department of Biochemistry, University of Melbourne

The proteasome as an antimalarial drug target

The *Plasmodium* proteasome represents a potential antimalarial drug target for compounds with activity against multiple life cycle stages. We have undertaken structural studies of the *Plasmodium* proteasome in complex with the PA28 activator. The structure of the *P. falciparum* PA28 regulator (*Pf*PA28) was solved by X-ray crystallography, revealing a heptameric bell-shaped structure. We purified *Pf*20S proteasome from parasite cultures and showed that *Pf*PA28 readily forms single and double capped complexes with *Pf*20S. Furthermore, we structurally characterised the *Pf*20S-*Pf*PA28 complex using cryo-EM.

In addition, we screened a library of human proteasome inhibitors (peptidyl boronic acids) and compared activities against purified *P. falciparum* and human 20S proteasome. We identified a series of potent parasite-active compounds that show a range of selectivity for inhibition of the growth of *P. falciparum* compared with human cell lines. To further validate the target, we selected *P. falciparum* for resistance *in vitro* to the clinically used boronate proteasome inhibitor, bortezomib. Whole genome sequencing revealed mutations in the proteasome β5 binding site. A medicinal chemistry program is currently underway to improve the specificity of inhibitors based on the hits we identified.

ALL WELCOME. Please join us for a light lunch after the seminar!
Further information: Matthew Dixon (matthew.dixon@unimelb.edu.au)