CBR

The Centre for Blood Research Seminar Series

Wednesday, March 9, 2016
LSC 3 - Life Sciences Centre
2350 Health Sciences Mall
12-1pm

Dr. Matthew Bogyo

Professor of Pathology and of Microbiology and Immunology and, by courtesy, of Chemical and Systems Biology, *Stanford University School of Medicine*

"Selective proteasome inhibitors as novel anti-malarial agents"

The proteasome is a multi-component protease complex responsible for regulating key processes such as the cell cycle and antigen presentation. Proteasome inhibitors have been shown to be toxic for the malaria parasite *Plasmodium falciparum* at all stages of its life cycle, including the transmissive gametocyte stages. However, all compounds that have been tested also inhibit the mammalian proteasome resulting in toxicity. We used a recently developed substrate profiling method to uncover differences in the specificities of the human and parasite 20S proteasome cores. We designed inhibitors based on amino acid preferences specific to the *P. falciparum* proteasome, and found that they preferentially inhibit the tryptic-like subunit β2. We determined the structure of the *P. falciparum* 20S proteasome bound to our inhibitor using cryo-EM and single particle analysis, to a resolution of 3.6 Å. These data reveal the unusually open *P. falciparum*□β2 active site and provide valuable information regarding active site architecture that can be used to further refine inhibitor design. Furthermore, we observed growth inhibition synergism with low doses of this β2 selective inhibitor in artemisinin (ART) sensitive and resistant parasites. Finally, we demonstrated that a parasite selective inhibitor attenuates parasite growth *in vivo* without significant toxicity to the host. Thus, the *Plasmodium* proteasome is a chemically tractable target for next generation anti-malarial agents.

Live Online Seminar Viewing:
http://tinyurl.com/cbrseminaronline

UBC a place of mind THE UNIVERSITY OF BRITISH COLUMBIA

Canadian Blood Services
it's in you to give

Health Canada Santé Canada