Contribution ID: **35** Type: **Oral**

Lactofungin and Amphotericin B Synergistically Interact with Model Membranes

Tuesday, 16 July 2024 15:30 (20 minutes)

Invasive fungal infections (IFIs) are an underappreciated public health threat that cause > 1.6 million deaths p/a with mortality rates between 20-80% [1,2]. Amphotericin B (AmB) is one of the most effective anti-fungal drugs. It kills fungal cells by binding to ergosterol in fungal cell membranes, causing membrane permeabilisation and changes in ergosterol-dependent signalling pathways [3 4]. Unfortunately, the structural similarity between ergosterol and cholesterol (mammalian cells) means AmB shows poor selectivity, resulting in dose-limiting toxicity causing severe side effects. Despite this, AmB remains a life-saving, last-resort drug because of its potent, broad-spectrum activity and low resistance rates [3]. There is a need to develop AmB-based treatments with reduced toxicity.

Recent work has revealed that the peptide Lactofungin (LFG) is synergistic with AmB. [5,6] LFG reduces the AmB dose 4 to 16-fold for many clinically relevant fungal pathogens. Recent work (Deplazes, unpublished) shows that LFG is non-toxic to human liver and kidney cells and non-haemolytic. This makes LFG a promising lead compound for developing an adjuvant drug that reduces the toxicity of AmB. We have shown that the synergy observed in cells can be reproduced in sterol-containing phospholipid bilayers, indicating the synergy is likely to be lipid dependent. Therefore model membrane systems can be used to elucidate the yet unknown mechanism of synergy.

Previous neutron reflectomtery experiments [7] have shown that at high concentrations AmB inserts into the lipid chain region of both pure POPC and sterol-containing membranes and does not significantly perturb the structure of pure POPC membranes. Furthermore AmB extracted ergosterol but not cholesterol, inserting more so into cholesterol-containing membranes. Our approach has been, initially, to reduce the AmB concentration 40 fold, closer to the clinically relevant dose and study the interactions with sterol containing membranes via a number of techniques including neutron reflectometry. Electrical impedance spectroscopy showed that LFG increases the AmB-induced disruption in an ergosterol-selective manner. Ultraviolet-visible spectroscopy and isothermal calorimetry show that, in contrast to Bovine Serum Albumin, the peptide LFG has negligible membrane binding and does not alter the solubility of AmB. This presentation will focus on our reflectivity work and outline future prospects.

References:

1. Fisher, M. C. & Denning, D. W. Nature Reviews Microbiology, 1-2 (2023).
2. Boroujeni, Z. B. et al. Microbial pathogenesis 152, 104616 (2021).
3. Cavassin, F. B. et al. Infectious Diseases and Therapy 10, 115-147 (2021)
4. Kamiński, D. M. European biophysics journal 43, 453-467 (2014).
5. Fernandes, K. E. & Carter, D. A. Frontiers in microbiology 8, 2 (2017).
6. Fernandes, K. E., Payne, R. J. & Carter, D. A. Antimicrobial Agents and Chemotherapy 64, e00842-00820 (2020).
7. Delhom R., Nelson A., Laux L., Haertlein M., Knecht W., Fragneto G. & Wacklin-Knecht H.P., nanomaterials, 2020, 10, 2439.

Please select the related topic from the list below

Biological membranes and interfaces

Primary authors: Ms HARTMANN, Lissy (University of Technology Sydney); HOLT, Stephen (Australian Nuclear Science and Technology Organisation)

Co-authors: Dr RUSSELL, Robert (Australian Nuclear Science and Technology Organisation); Ms PEREIRA SCHMIDT, Anneka (University of Queensland); Ms CHAVALI, Chandra (University of Queensland); Dr CRANFIELD, Charles (University of Technology Sydney); Dr DEPLAZES, Evelyne (University of Queensland)

Presenter: HOLT, Stephen (Australian Nuclear Science and Technology Organisation)

Session Classification: Biological membranes and interfaces