McGill

Department of Anatomy and Cell Biology

Seminar Series

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Hosted by: Natalie Zeytuni, Ph.D.

Wednesday, Nov. 30, 2022
11:30 am -12:30 pm
Room 1/12 - Strathcona Anatomy and Dentistry Building

"The architecture of an emerging source of antibiotic resistance"

We investigate the prevalence and evolutionary origin of an emerging antibiotic resistance enzyme and track its modern context in multi-drug resistance contexts carried in pathogenic microbes. DfrB enzymes were first identified in the 1970's for providing resistance to the antimicrobial trimethoprim due to their dihydrofolate reductase activity. Their SH3 fold forms an active enzyme upon homotetramerisation. Intriguingly, DfrB enzymes have no evolutionary homology to any characterized protein, such that their evolutionary origin is unknown. Computational exploration of the DfrB sequence space suggests that DfrB probably originated in Alphaproteobacteria. Through kinetic characterization, negative-stain electron microscopy and further biophysical characterization, we have demonstrated that structurally diverse, putative proteins sharing with DfrB only its SH3 fold, homotetramerize to recreate the DfrB active site environment and provide high trimethoprim resistance. Our results contribute important insights into the evolutionary path that finds the SH3-like fold of DfrB enzymes included in the modern resistome.