MICROBIOLOGIE, INFECTIOLOGIE ET IMMUNOLOGIE

CONFERENCE

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Room N-833
Université de Montréal, Pavillon Roger-Gaudry.
2900 boul. Édouard Montpetit (Chemin de la tour), Montréal.

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The influence of microbial interactions in developing therapeutic strategies that target biofilm-forming microorganisms

Chronic pulmonary diseases including cystic fibrosis (CF) are a heterogenous group of chronic inflammatory diseases of the airways associated with distinct microbial profiles. The CF airways are successively colonized with Gram-positive bacterium *Staphylococcus aureus*, Gram-negative bacterium *Pseudomonas aeruginosa* and mold *Aspergillus fumigatus*. These species are capable of a mixed-species sessile lifestyle embedded in self-produced matrices, known as biofilms, that can be less susceptible to antibiotics. My work has leveraged microbial interactions in developing therapeutic strategies against microbial biofilms including antibiofilm agents, mining for antimicrobial-like molecules, and antimicrobial delivery.

Biofilm formation by *A. fumigatus* and *P. aeruginosa* is supported by the production of the structurally similar cationic exopolysaccharides galactosaminogalactan (GAG) and Pel, respectively. We demonstrated the potential for these organisms to use these exopolysaccharides to form co-operative biofilms. Further, recombinant glycoside hydrolases (GH)s that degrade biofilm exopolysaccharides were evaluated as antibiofilm agents in mouse models of invasive aspergillosis or *P. aeruginosa* infection. Intratracheal GH administration was well tolerated by mice. GH prophylaxis resulted in reduced fungal burden in mice. Combining GH prophylaxis with the antifungal posaconazole or the antibiotic ciprofloxacin resulted in a greater reduction in fungal or bacterial burden than with either agent alone. This study laid the foundation for further exploration of GH therapy in mixed fungal-bacterial infections.

The majority of available antimicrobials are derived from soil and marine dwelling Actinobacteria known to produce structurally diverse natural products as secondary metabolites. Microbial interactions can induce the production of secondary metabolites. These secondary metabolites include ribosomally synthesized and post-translational modified peptides (RiPPs). The lanthionine-containing peptides (lanthipeptides) are a subclass of RiPPs with cross-linked dehydroamino acids through thioether bonds. Here, we used a combination of LC/MS, HPLC and bioinformatics (AntiSMASH) to investigate co-cultures of marine Streptomyces-Actinomycetes species for bioactive secondary metabolites encoded in silent biosynthetic gene clusters. We detected and solved the secondary structure of a novel class I lanthipeptide. Spot assays demonstrated inhibitory activity against *P. aeruginosa*, a novel finding, as known lanthipeptides target Gram-positive bacteria.

Membrane vesicles (MV)s are bacterial-derived spherical nanostructures composed of a lipid bilayer that encapsulates cytoplasmic, periplasmic, and outer membrane biomolecules that are released by most Gram-positive and -negative bacteria. Exogenous MVs can modulate single-species biofilm formation. MVs hold potential as drug delivery carriers, as MVs can transport large biomolecules including antibiotics and fuse with the outer membrane of Gram-negative bacteria to deliver their cargo. A four CF-species biofilm community model of *P. aeruginosa, S. aureus, Streptococcus sanguinis,* and *Prevotella melaninogenica* has been developed. Here, with electroporation we will optimize antibiotic vancomycin loading of MVs and engineer MVs with matrix degrading enzymes to evaluate the effectiveness of MV-mediated delivery of vancomycin against *P. aeruginosa* and in the disruption of the CF-species biofilm model.