Bilayers at the ILL

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Drug delivery of antimicrobial peptides to lipid bilayers

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The rise of antimicrobial resistance is a major challenge for future healthcare needs. To date antibiotic resistant bacterial strains have been reported in every country with prevalence growing annually. One promising line of treatment is antimicrobial peptides (AMPs), small cationic peptides, similar to the innate antimicrobial peptide defense in humans. It has been shown that AMPs can be highly selective and potent towards bacterial membranes through the disruption of the lipid envelope. However, AMPs are particularly susceptible to proteolytic degradation and decreased bioavailability, thereby challenging their widespread therapeutic use. It is important to protect AMPs from proteolytic degradation whilst maintaining a potent release profile.
In this project, we have focused on two possible drug delivery vehicles, lipid cubosomes and microgels. Both vehicles protect the AMPs from degradation whilst maintaining the desired bacteria killing effects. We have used a common model AMP, LL-37, and studied its interaction, as a function of concentration, with model lipid bacterial membranes composed of dimyristoylglycerophosphocholine (DMPC) and dimyristoylglycerophosphoglycerol (DMPG). At low concentrations LL-37 inserted into the tail region of the bilayer, predominately in the outer leaflet. At therapeutically relevant concentrations, LL-37 was found to span the lipid bilayer, removing lipids and causing pore formation. We compared this effect to that of the AMP loaded into either glycerol monoleate cubosomes or poly(ethyl acrylate-co-methacrylic acid) (MAA) microgels. Both drug delivery vehicles have shown promising results in bacteria killing assays, however, the effect of the vehicle on the AMP mode of action was not previously known. In neutron reflection experiments AMP-loaded cubosomes were found to bind directly to the bilayer, inserting both cubosome material and AMPs to the lipid bilayer.[1] MAA microgels acted as passive protective containers, lowering the free LL-37 concentration but not interacting directly with the bilayer. [2]

1. L. Boge, K.L. Browning, R. Nordström, M. Campana, L.S.E. Damgaard, J. Seth Caous, M. Hellsing, L. Ringstad, M. Andersson. *ACS Appl. Mater. Interfaces.* 11 (2019) 21314–21322.
2. R. Nordström, K. Browning, E. Parra-Ortiz, L. S. E. Damgaard, S. Malekkhaiat-Häffner, R. A. Campbell, J. Cooper, M. Malmsten. *manuscript in preparation*

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