nonlethal membrane effects on the majority of bacteria (Hakansson et al. 2000, 2011). HAMLET was first shown to sensitize *Streptococcus pneumoniae* to several classes of antibiotics (penicillin, macrolides, and aminoglycosides) in the presence of sublethal concentrations of HAMLET (Marks et al. 2012). The sensitizing activity was shown through a decreased MIC value for penicillin and erythromycin-resistant pneumococci that are listed on the WHO priority pathogen list. Furthermore, HAMLET provided a strong sensitizing effect both against biofilms and in an *in vivo* nasopharyngeal colonization model, where bacterial eradication was observed only after combination treatment with HAMLET and antibiotics. In a similar fashion, HAMLET was also shown to sensitize the priority pathogens *A. baumannii* and *S. aureus* to a broad range of antibiotics both *in vitro* and for *S. aureus* also *in vivo* (Marks et al. 2012, 2013). As HAMLET is a natural compound obtained from human milk, the risk of cytotoxicity and other adverse effects is low. Another promising quality of HAMLET is its wide range of activity – a result from potentially targeting highly conserved pathways in bacteria that bacteria cannot survive without. This could make HAMLET applicable as an adjuvant in treatment of many different clinically important and difficult to treat multidrug-resistant infectious diseases.

Additional compounds that affect membrane potential and proton motive force have been described. In a screen of non-antibiotic drugs, Ejim et al., found that loperamide, used as over the counter medication against diarrhea, showed a sensitizing activity for minocycline against *P. aeruginosa* (Ejim et al. 2011). Loperamide dissipated the electrical component the proton motive force in the bacteria, leading to an increased pH gradient over the inner membrane that increased the uptake of antibiotics into the cells. In a different study, compounds were identified that dissipated the proton motive force in methicillin-resistant *S. aureus* (MRSA) (Farha et al. 2013). By mixing compounds that affected the electrical gradient and the pH gradient over the membrane, a synergistic effect was obtained that lowered the concentrations of the drugs to a level where toxicity to human cell were not detected and only antibiotic sensitization was observed (Farha et al. 2013). Finally, in a study by Balakrishna et al., acyl polyamines were shown to bind to Gram-negative bacteria and increase their membrane permeability (Balakrishna et al. 2006). Unfortunately, these polyamines are potentially cytotoxic, making some of them unfit for clinical use. However, albumin in blood lowers this cytotoxicity, making polyamines interesting for future research.

In conclusion, attacking the membrane potential and the proton motive force to both affect the energetics of the bacteria and increase permeability of antibiotics over the membrane, although wrought with some potential toxicity problems, appears to be a strategy that can be well tolerated and effective clinically in the near future.