Lipophosphonoxins – Novel Membrane Targeting Antimicrobials

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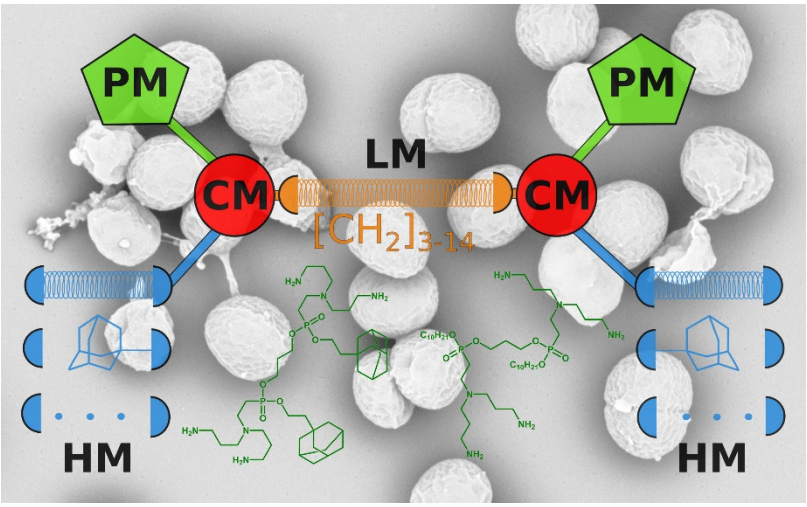
Abstract

The alarming rise of bacterial antibiotic resistance requires the development of new compounds. Such compounds, lipophosphonoxins (LPPOs), were previously reported to be active against numerous bacterial species but serum albumins abolished their activity.[1,2]

Here we report synthesis and evaluation of novel antibacterial compounds termed LEGO-LPPOs, based on LPPOs, consisting of a central linker module with two attached connector modules on either side.[3] The connector modules are then decorated with polar and hydrophobic modules. We performed an extensive structure-activity relationship study by varying the length of the linker and hydrophobic modules. The best compounds were active against both Gram-negative and -positive species including multiresistant strains and persisters. LEGO-LPPOs act by first depleting the membrane potential and then creating pores in the cytoplasmic membrane. Importantly, their efficacy is not affected by the presence of serum albumins. Low cytotoxicity and low propensity for resistance development demonstrate their potential for therapeutic use.

Application of original LPPOs in an active wound dressing based on the polycaprolactone nanofiber scaffold (NANO) is also discussed.[4] We demonstrated in vitro that LPPO released from NANO exerted antibacterial activity while not impairing proliferation/differentiation of fibroblasts and keratinocytes. Secondly, using a mouse model we showed that NANO loaded with LPPO significantly reduced the Staphylococcus aureus counts in infected wounds as evaluated 7 days post-surgery. The rate of degradation and subsequent LPPO release in infected wounds was facilitated by lytic enzymes secreted by inoculated bacteria. Finally, LPPO displayed negligible to no systemic absorption. In conclusion, the composite antibacterial NANO-LPPO-based dressing reduces the bacterial load and promotes skin repair, with the potential to treat wounds in clinical settings.

Keywords: resistance, antibacterial, lipophosphonoxine, cellular membrane, nanomaterial



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