Liposomal delivery of oligonucleotide therapeutics against antibiotic-resistant bacteria

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Microbial resistance to antibiotics has grown over the last few decades into a serious global threat [1], which must be tackled with innovative therapeutics. We propose to address it by coupling the action of a strong antibacterial, the bolaform cationic surfactant [12-bis-THA]Cl_2, with specifically engineered oligonucleotides (TFDs, Transcription Factor Decoys) that can block essential genomic targets in bacteria [2,3]. In order to improve the bioavailability and antibacterial activity of the [12-bis-THA]Cl_2/TFD complex, we incorporated it in fusogenic liposomal carriers with controlled composition and morphology. We investigate the effect of the inclusion of the bolaamphiphile in the lipid bilayer and optimize the encapsulation of the oligonucleotide. We characterize the structure of the liposomes by means of dynamic light scattering (DLS), Zeta potential measurements, small-angle X-ray scattering (SAXS), cryogenic electron microscopy (cryo-TEM), UV-Vis absorption and fluorescence spectroscopy. The antibacterial activity and cytotoxicity of these delivery systems are evaluated with *in vitro* assays, while confocal microscopy experiments on fluorescently labelled samples allow us to assess the delivery of the TFD into model bacterial systems (Figure 1).

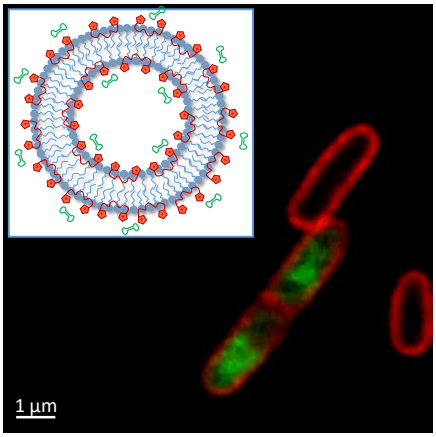

Figure 1 Confocal microscopy: liposomes containing the [12-bis-THA]Cl_2/TFD complex (green) are delivered into *E. coli* (red). Insert: schematic representation of the liposomes (blue = POPC/DOPE, red = [12-bis-THA]Cl_2, green = TFD.

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