Nanoparticulate oligonucleotides for the treatment of drug-resistant pathogens

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Increasing threat of antimicrobial resistance to antibiotics requires new strategies for drug developing. DNA-based therapeutics such as transcription factor decoys (TFDs)[1] are promising agents in the treatment of bacterial infections. Due to their strong instability *in vivo* as well as a low intracellular uptake, new strategies of delivery to bacterial cells are strongly required. It has been shown that aliphatic bolaamphiphiles cationic compounds, like the 10,10'-(dodecane-1,12-diyl)bis(9-amino-1,2,3,4-tetrahydroacridin-10-ium) (12-bis-THA): i) self-assemble with oligonucleotides, ii) are able to protect them against DNAse/RNAse activity[2,3] and iii) deliver them into bacteria. Here, the ability of 12-bis-THA to efficiently bind and protect TFDs have been evaluated by Dynamic Light Scattering (DLS), fluorescence spectroscopy (SYBR Green) and agarose gel electrophoresis. The interaction with bacteria and the ability to deliver TFDs in both G+ and G- bacteria were evaluated by confocal microscopy.

NP biodistribution of radiolabelled compounds in healthy mice, show that LNPs mainly accumulate in liver and kidneys. Moreover, by modulating the 12-bis-THA to TFD ratio, blood permanence and affinity with the lung can be increased. Histopathological studies after H&E staining of target tissues, showed no apparent toxicity in treated animals.

In conclusion, we show that 12-bis-THA is a very promising agent to deliver DNA-based therapeutics to bacterial cells in vitro and in vivo.

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