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Development of a Novel Antibacterial to Block Growth of Pseudomonas Aeruginosa and Prevent Biofilm Formation

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Abstract : Cystic fibrosis (CF) is an autosomal recessive genetic disorder characterized by abnormal transport of chloride and sodium across the lung epithelium, leading to thick and viscous secretions. Within which CF patients suffer from repeated bacterial pulmonary infections, with Pseudomonas aeru-ginosa (PA) eliciting the greatest inflammatory response, causing an irreversible loss of lung func-tion that determines morbidity and mortality. The cell wall of PA is a permeability barrier to many antibacterials and the rise of Mutli-Drug Resistant strains (MDR) is eroding the efficacy of the few remaining clinical options. In addition when PA infection becomes established it forms an antibi-otic-resistant biofilm, embedded in which are slow growing cells that are refractive to drug treat-ment. Making the development of new antibacterials a major challenge. This work describes the development of new type of nanoparticulate oligonucleotide antibacterial capable of tackling PA infections, including MDR strains. It is being developed to both block growth and prevent biofilm formation. These oligonucleotide therapeutics, Transcription Factor Decoys (TFD), act on novel genomic targets by capturing key regulatory proteins to block essential bacterial genes and defeat infection. They have been successfully transfected into a wide range of pathogenic bacteria, both in vitro and in vivo, using a proprietary delivery technology. The surfactant used self-assembles with TFD to form a nanoparticle stable in biological fluids, which protects the TFD from degradation and preferentially transfects prokaryotic membranes. Key challenges are to adapt the nanoparticle so it is active against PA in the context of biofilms and to formulate it for administration by inhalation. This would allow the drug to be delivered to the respiratory tract, thereby achieving drug concentrations sufficient to eradicate the pathogenic organisms at the site of infection.

Keywords : antibacterials, transcriptional factor decoys (TFDs), pseudomonas aeruginosa
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