Technology Opportunity

Ref: RDLP# 840

Keywords: antimicrobial, bacteria, biofilm, antibiotics, peptides

BACKGROUND:

Cystic fibrosis (CF) is the most common fatal inherited disorder in the Caucasian population, affecting 100,000 patients worldwide. Despite an extensive treatment burden, CF patients succumb to lung failure caused by chronic bacterial infection, principally *Pseudomonas aeruginosa* (Pa). With tobramycin resistance in the CF lung rising from 5% in 1998 to over 20% today, control of chronic Pa infection is a major clinical unmet need for these patients.

The arsenal of antibiotics for Pa in CF is very limited, with the leader being a dry powder inhaled formulation of tobramycin at a yearly cost/patient of ~$30,000, with 80% of adult CF patients on the drug. Most conventional antibiotics are ineffective in the CF lung due to the thick mucoid environment and the tendency of *Pseudomonas* to form impermeable biofilms.

DESCRIPTION OF THE INVENTION:

Despite considerable effort in the past few decades, no new therapeutics for the treatment of CF-related infections have made it to the market. Consequently, there are only a handful of interventions to target CF infection in the current pipeline. The main reason for past failures has been the lack of efficacy and safety. SickKids researchers have developed a series of cationic antimicrobial peptides (CAPs) that on their own physically disrupt bacterial membranes and their previously impermeable biofilms (Figure 1), leading to cell lysis and death, and thus unlikely to evoke resistance. Also, CAPs in combination with first line antibiotics demonstrates a synergistic effect compared to each compound’s effect when used separately (Figure 2).

The researchers have shown that the CAPs...
- Are active at low MICs (i.e., 2 µM) against Pa and other bacteria.
- Are non-hemolytic in host erythrocytes and non-toxic to mammalian cells.
- Show excellent activity against clinical isolates of *P. aeruginosa* from CF patients.

The issue of efficacy arises from the fact that Pa strains that infect the lungs create biofilms and hence significantly reduce the efficacy of antibiotics. Furthermore, during chronic lung infection Pa can develop resistance to the commonly-used antibiotics. SickKids technology overcomes these limitations by exerting its antimicrobial effect through a mechanism that Pa cannot develop tolerance against, while at the same time weakening the Pa biofilm and thereby increasing the efficacy of existing antibiotics.

**POTENTIAL ADVANTAGES/APPLICATIONS**

The properties of our lead CAP (a 17-residue lysine-rich peptide) may be summarized as follows:

- Water-soluble and stable over long time periods in solution or in lyophilized form.
- Straightforward to produce in high yields (routine lab-scale runs yield 20-30 mg of purified peptide).
- Minimum inhibitory concentrations (MICs) in the range of 2-4 µM against several bacteria.
- Highly selective for bacterial membranes vs. host membranes; non-hemolytic at high doses (> 300 µM) in human red blood cells.
- Non-toxic to other mammalian cells up to > 100 µM.
- Able to cause killing of planktonic bacteria more rapidly than conventional antibiotics (such as tobramycin, ciprofloxacin, and merepenem).
- Able to potentially disrupt the anionic polymeric sugar ‘barriers’ (exopolysaccharides) of bacterial biofilms.
- Active against resistant clinical strains of *P. aeruginosa* on its own (including tobramycin resistant strains); when used in combination therapy experiments (with antibiotics) on CF clinical isolates, able to produce significant zones of killing (‘synergy’) with both planktonic and biofilm forms of this bacterium.
- Unlikely to evoke resistance due its membrane-lytic mechanism of action.
- Tolerated in toxicity evaluation in female CD-1 mice up to 3.7 mg/kg (calculated as 10 x MIC = 40 µM in blood).
DEVELOPMENTAL STAGE: Pre-clinical in vitro data.

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PATENT STATUS: US and Canadian patent applications have been filed.


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