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# Development of BMAP18 as a peptide drug in the lung bacterial infections: a study to improve its effectiveness in the CF-pulmonary environment

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**Background.** Cystic fibrosis (CF) patients must deal with pulmonary bacterial infections by antibiotic-resistant pathogens. A weapon that could be used against pulmonary infections are antimicrobial peptides (AMPs), natural molecules with antibiotic activity. The BMAP18 peptide has a potent antibacterial in vitro activity, however it could not protect mice with P. aeruginosa infection and showed quite toxic side effects.

**Hypothesis & Objectives.** Because of these problems which are common to many others AMPs, BMAP18 could not be directly used in clinic. Our aim was to investigate the reasons of toxicity and scarce activity of BMAP18 in mice model of infection to optimize the molecule for its usage in the particular lung environment of CF patients. Tobramycin and colistin antibiotics have been used for comparison.

**Methods.** Specific conditions have been used in order to mimic the amount of DNA and mucin of the CF lung and a mice bronco-alveolar lavage, to evaluate the antimicrobial activity of BMAP18 and its stability in this specific environment. A modified peptide, D-BMAP18, has been synthesized. It has been tested for its antimicrobial activity and stability and then in vivo administered to healthy mice to evaluate its toxicity and to mice with a pulmonary infection to assess its therapeutic potential.

**Results.** We detected a reduced activity of BMAP18 and tobramycin due to DNA and mucin. In addition, we observed that the peptide is degraded in the lung bronchoalveolar lavage in mice, explaining the scarce antimicrobial effect previously observed in vivo. For this reason a stereoisomeric form of the peptide, D-BMAP18, resistant to proteolytic degradation was prepared and tested. D-BMAP18 maintained its in vitro activity, and when used on a pulmonary acute infection healthy mice or with acute pulmonary infection by a P. aeruginosa stain the peptide showed to be almost active as tobramycin.

**Spin-off for research & clinical purposes.** The effectiveness of D-BMAP-18 could be increased further whether the components of bronchoalveolar lavage that inhibit the activity of the peptide without degrading it will be identified. These results not only bring clinical applications of D-BMAP closer, but also draw a method of study which could be also applied to other AMPs.



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