Combating multidrug-resistant bacterial infections with peptide-loaded lipid-polymer hybrid nanoparticles

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Antimicrobial resistance is a global health concern that is rising to dangerously high levels. Antimicrobial peptides (AMPs) have emerged as promising alternatives to antibiotics due to their high efficacy and low resistance rates against several bacterial strains[1]. However, the clinical application of AMPs is hampered by their toxicity, immunogenicity and rapid degradation *in vivo*. This study aims to develop a novel AMP delivery system based on non-toxic and non-immunogenic nanocarriers with tunable physicochemical properties to improve the stability and therapeutic efficacy of AMPs *in vivo*.

Lipid-polymer hybrid nanoparticles (LPNPs) that combine the advantages of both liposomes and polymeric nanoparticles[2] were developed for the encapsulation of two antimicrobial peptides, cathelicidin (LL-37) and Human beta-defensin 3 (hBD3). These peptides present the main defense response of the respiratory system and are known for their broad-spectrum antibacterial activity against multidrug-resistant Gram+ and Gram- bacterial strains[3].

The peptide-loaded LPNPs were prepared by emulsion-solvent evaporation method using both sonication and microfluidic mixing. The formulations were characterized for their physicochemical characteristics (DLS), their morphology (AFM, TEM), as well their stability after lyophilization and storage under different conditions. Finally, their antimicrobial efficacy towards *E. Coli* and *B. Subtilis*, was tested and compared to the peptide solutions.

The LPNP formulations that were developed demonstrated an optimal size (~150 nm), and polydispersity index (PDI < 0.2) with a spherical morphology. Compared to liposomes, they maintained their physicochemical characteristics after lyophilization and storage in different temperatures. In addition, they demonstrated enhanced antimicrobial activity towards the *E. Coli* and *B. Subtilis* bacterial strains.

In summary, a novel lipid-polymer hybrid nanoparticle system was developed that exhibited optimal physicochemical properties, stability and improved antimicrobial efficacy compared to the peptide solutions, indicating that they could be an important alternative tool for the fight against bacterial resistance. Further *in vitro* and *in vivo* studies are needed to exploit the potential of this novel LPNP system.

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