Empowering Antibiotics in the AMR Landscape: Insights from Dendrimer Conjugation in ALI systems

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In the shadow of the AMR crisis, reigniting antibiotic discovery has emerged as a pivotal strategy. Despite the urgent need, there has been a decrease in creating new types of antibiotics over the past forty years. Of the 65 antibiotics introduced in the last two decades, only four were genuinely new pharmacological classes, whilst the remainder were merely derivatives or modifications of pre-existing compounds. This challenge arises from the need to bypass bacterial resistance, which, paradoxically, is also the target.

Inspired by a 2006 study that successfully integrated propranolol with a known drug delivery polymer, DAB-PAMAM dendrimer, for enhanced cellular uptake, we advanced this approach by conjugating the antibiotic ciprofloxacin with PAMAM dendrimers. This strategy aims to enhance the antibiotic's effectiveness by preventing its ejection from cells.

The screening results were promising *Escherichia coli* showed MIC values of 1.25 µg/µl, while *Pseudomonas aeruginosa* stood at 1-2 µg/µl. Interestingly, *Staphylococcus aureus* exhibited slightly elevated values, oscillating between 2-4 µg/µl. MIC values varied by a factor of 2 when tested in media other than MHB. The compounds did not result in cytotoxicity or hemolysis.

However, we have learned, that tackling AMR requires not only the identification of suitable candidates, but also ensuring that standardized screening methodologies are in congruence with clinical needs.

Therefore, we employed an air-liquid interface (ALI) culture set-up to mimic respiratory epithelial cells' natural environment. By introducing *P. aeruginosa* and *S. aureus,* we sought to compare their behavior with standard lab screenings, aiming to bridge the gap between conventional lab methods and clinical needs inside the antimicrobial development pipeline.