Combinatorial Discovery of Broad Spectrum Antimicrobial Peptide Dendrimers

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Multi-drug resistant bacteria (MDR) are major threat to public health and lead to untreatable infections. Notable pathogens include Gram-negatives such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* and Gram-positives such as Methicillin-resistant *Staphylococcus aureus* (MRSA). We have recently reported that peptide dendrimers with multiple cationic and hydrophobic groups can exert potent antibacterial effects by a membrane disruptive effect.[1] However, our most active antimicrobial peptide dendrimer (AMPD) **G3KL** was 37 residues in size and was therefore too large for practical application. Here we focused on discovering much smaller AMPDs using our previously reported combinatorial approach to peptide dendrimers.[2] We prepared a combinatorial library of potentially membrane active peptide dendrimers on a photolabile support[3, 4] and screened them for antimicrobial activity against *P. aeruginosa* using an agar-plate assay tailored for library screening.[5] Bead decoding, resynthesis and testing revealed several particularly potent antimicrobial peptide dendrimers (AMPDs). These AMPDs are much smaller than our previous best compound **G3KL** yet also act by a membrane disruptive mechanism similar to that of polymyxin. Most remarkably, our new AMPDs can be readily prepared in large scale with excellent isolated yields, and show activity against both Gram positive and Gram negative MRD strains including MRSA.

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