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The Antimicrobial Activity of Peptide Dendrimers and Polymyxin B Increases Sharply Above pH 7.4

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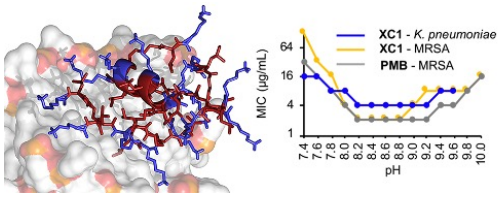
Recently we reported antimicrobial peptide dendrimer (AMPD) G3KL and T7 with potent activities against P. aeruginosa and A. baumannii, two of the most problematic antibiotic-resistant nosocomial pathogens[1][2]. In our efforts to develop new AMPDs against Gram-negative bacteria, we investigated their activity at acidic and basic pH, which correspond to the conditions of the site of bacterial infections on skin or biofilms and chronic wounds respectively. Removing the eight low pKa amino termini by substituting the N-terminal lysine residues with aminohexanoic acid in our reference dendrimer G3KL provided the modified peptide dendrimer XC1 with a broader pH-activity range. Furthermore, we discovered that raising the pH to 8.0 reveals strong activities against Klebsiella pneumoniae and methicillin at pH 7.4, an effect also observed with polymyxin B and tentatively assigned to stronger binding to the bacteria at higher pH as observed with a fluorescence labeled dendrimer analog. This work has been published in Chemical Communication.[3]



[1] M. Stach, T. N. Siriwardena, T. Köhler, C. van Delden, T. Darbre, and J.-L. Reymond, “Combining Topology and Sequence Design for the Discovery of Potent Antimicrobial Peptide Dendrimers against Multidrug-Resistant *Pseudomonas aeruginosa*,” *Angew. Chem. Int. Ed.*, vol. 53, no. 47, pp. 12827–12831, Nov. **2014**, doi: 10.1002/anie.201409270.

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[3] X. Cai, S. Javor, B.-H. Gan, T. Kohler, and J.-L. Reymond, “The Antibacterial Activity of Peptide Dendrimers and Polymyxin B Increases Sharply Above pH 7.4,” *Chem. Commun.*, p. 10.1039.D1CC01838H, **2021**, doi: 10.1039/D1CC01838H.