

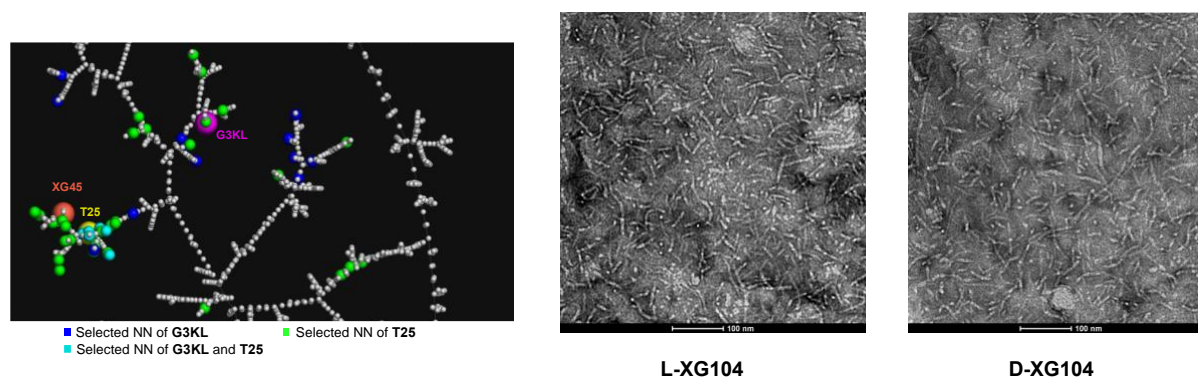
Stereorandomized Antimicrobial peptide dendrimers from Chemical Space against multidrug-resistant bacteria

Xingguang Cai, Markus Orsi, Alice Capecchi, Sacha Javor, Jean-Louis Reymond

Department of Chemistry, Biochemistry and Pharmaceutical Sciences, University of Bern, Freiestrasse 3, CH-3012, Bern, Switzerland

Nearest neighbours (NN) searching in virtual libraries has been a utility tool for optimizing antimicrobial peptides (AMPs).¹ AMPs are promising candidates as antibacterial agents.² Our group previously discovered that stereorandomized peptides had reduced hemolysis while preserving antimicrobial activities.³ However NN searching has not been performed in stereorandomized antimicrobial peptides chemical space.

Herein, we selected 63 new analogs of stereorandomized AMP T25 selected as nearest neighbour (NN) in chemical space by similarity using the MXFP fingerprint. Synthesis and testing of 63 stereorandomized analogs pointed to a new AMP XG45. We then further modified this dendrimer by removing its N-termini to form AMP XG104 inspired by our previous pH dependent study.⁴ Both XG45 and XG104 showed good potency against a panel of Gram-negative bacteria at pH 7.4 and 8.0 and activity against MRSA at pH 8.0. Interestingly, the homochiral all L- and all D- versions of both XG45 and XG104 are not antibacterial but strongly hemolytic, this unusual finding indicates that stereorandomization not only can reduce hemolysis but also can confer antibacterial activity.



[1] Capecchi, A.; Reymond, J.-L. Peptides in Chemical Space. *Med. Drug Discov.* 2021, 9, 100081. <https://doi.org/10.1016/j.medidd.2021.100081>.

[2] Magana, M.; Pushpanathan, M.; Santos, A. L.; Leanse, L.; Fernandez, M.; Ioannidis, A.; Giulianotti, M. A.; Apidianakis, Y.; Bradfute, S.; Ferguson, A. L.; Cherkasov, A.; Seleem, M. N.; Pinilla, C.; de la Fuente-Nunez, C.; Lazaridis, T.; Dai, T.; Houghten, R. A.; Hancock, R. E. W.; Tegos, G. P. The Value of Antimicrobial Peptides in the Age of Resistance. *Lancet Infect. Dis.* 2020, 20 (9), e216–e230. [https://doi.org/10.1016/S1473-3099\(20\)30327-3](https://doi.org/10.1016/S1473-3099(20)30327-3).

[3] Siriwardena, T. N.; Gan, B.-H.; Köhler, T.; van Delden, C.; Javor, S.; Reymond, J.-L. Stereorandomization as a Method to Probe Peptide Bioactivity. *ACS Cent. Sci.* 2021, 7 (1), 126–134. <https://doi.org/10.1021/acscentsci.0c01135>.

[4] Cai, X.; Javor, S.; Gan, B. H.; Köhler, T.; Reymond, J.-L. The Antibacterial Activity of Peptide Dendrimers and Polymyxin B Increases Sharply above PH 7.4. *Chem. Commun.* 2021, 57 (46), 5654–5657. <https://doi.org/10.1039/D1CC01838H>.