Stereorandomization as a Method to Probe Peptide Bioactivity

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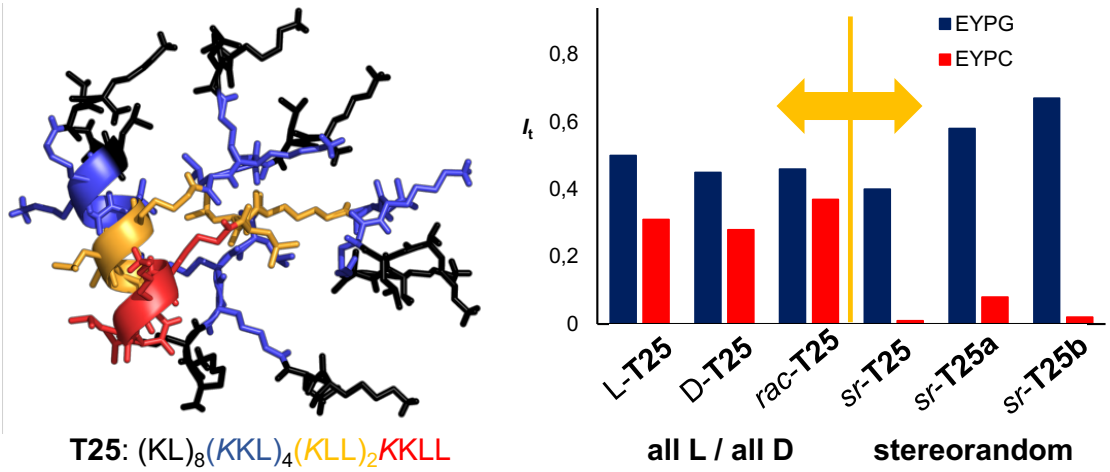
Peptides and proteins consist of chains of homochiral amino acids. L-chirality prevails in ribosomally synthesized peptides, but both L- and D-residues occur in peptides from non-ribosomal and chemical peptide synthesis. D-residues are often installed to increase stability against proteases. Herein we explore stereorandomized (sr) peptides containing up to billions of different stereoisomers, which we obtain as well-defined single HPLC peak, single mass products by using racemic amino acids in solid-phase peptide synthesis. We investigate sr-analogs of antimicrobial peptides and peptide dendrimers. We discover that partial or complete stereorandomization protects from proteolysis in serum, modulates antimicrobial and antibiofilm activity, and can reduce hemolysis and cytotoxicity, thereby revealing the role of peptide secondary structures in activity. Stereorandomization should be generally useful to study and improve the properties of peptides.



1) T.N. Siriwardena, B. H. Gan, T. Köhler, C. Van Delden, S. Javor, J.L. Reymond, ACS Cent. Sci. 2021 (https://doi.org/10.1021/acscentsci.0c01135).