

## Stereorandomized peptide dendrimer from chemical space had reduced hemolysis and promoted antimicrobial potency

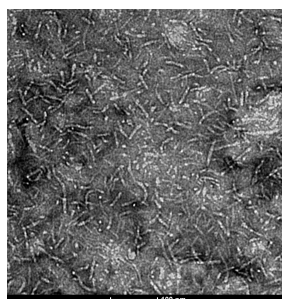
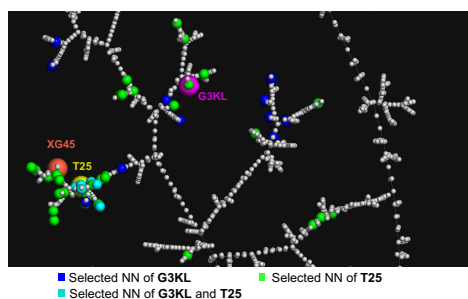
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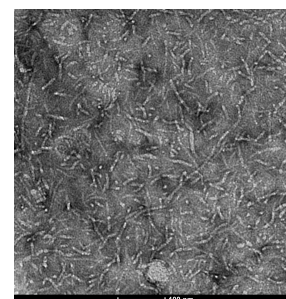
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Nearest neighbors (NN) searching in virtual libraries has been a utility tool for optimizing antimicrobial peptides (AMPs)<sup>1</sup>. AMPs are promising candidates as antibacterial agents.<sup>2</sup> Our group previously discovered that stereorandomized peptides had reduced hemolysis while preserving antimicrobial activities.<sup>3</sup> 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 neighbor (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<sup>4</sup>. 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.



L-XG104



D-XG104

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