Simulation-Guided Rational de Novo Design of a Small Pore-Forming Antimicrobial Peptide.

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In the age of failing small-molecule antibiotics, tapping the near-infinite structural and chemical repertoire of antimicrobial peptides (AMPs) offers one of the most promising routes toward developing next-generation antibacterial compounds. One of the key impediments en route is the lack of methodologies for systematic rational design and optimization of new AMPs. Here we present a new simulation-guided rational design approach and apply it to develop a potent new AMP. We show that unbiased atomic detail molecular dynamics (MD) simulations are able to predict structures formed by evolving peptide designs enabling structure-based rational fine-tuning of functional properties. Starting from a 14-residue poly leucine template we demonstrate the design of a minimalistic potent new AMP. Consisting of only four types of amino acids (LDKA), this peptide forms large pores in microbial membranes at very low peptide-to-lipid ratios (1:1000) and exhibits low micromolar activity against common Gram-positive and Gram-negative pathogenic bacteria. Remarkably, the four amino acids were sufficient to encode preferential poration of bacterial membranes with negligible damage to red blood cells at bactericidal concentrations. As the sequence is too short to span cellular membranes, pores are formed by stacking of channels in each bilayer leaflet.

Short bio:
Charles H. Chen is a Ph.D. candidate in Chemistry at King's College London under Dr. Martin Ulmschneider's supervision. He started his research interest in biotechnology as an undergraduate student in chemical engineering at Michigan State University. In 2013, he joined Dr. Ulmschneider's lab at Johns Hopkins University as a Ph.D. candidate in materials science and engineering, and moved with the lab and continued his Ph.D. study in London in 2017. During his Ph.D. journey, he applied both computational and experimental techniques to understand how peptides selectively bind, fold and assemble in cell membranes, and thus kill the cells. Charles' career goal is to combine interdisciplinary techniques and develop promising therapeutic biologics to fight cancers, infectious diseases, and rare diseases.