

Abstract Submitted
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Synthetic Molecular Evolution of Membrane-Active Peptides

WILLIAM WIMLEY, Tulane Univ Med Sch — The physical chemistry of membrane partitioning largely determines the function of membrane active peptides. Membrane-active peptides have potential utility in many areas, including in the cellular delivery of polar compounds, cancer therapy, biosensor design, and in antibacterial, antiviral and antifungal therapies. Yet, despite decades of research on thousands of known examples, useful sequence-structure-function relationships are essentially unknown. Because peptide-membrane interactions within the highly fluid bilayer are dynamic and heterogeneous, accounts of mechanism are necessarily vague and descriptive, and have little predictive power. This creates a significant roadblock to advances in the field. We are bypassing that roadblock with synthetic molecular evolution: iterative peptide library design and orthogonal high-throughput screening. We start with template sequences that have at least some useful activity, and create small, focused libraries using structural and biophysical principles to design the sequence space around the template. Orthogonal high-throughput screening is used to identify gain-of-function peptides by simultaneously selecting for several different properties (e.g. solubility, activity and toxicity). Multiple generations of iterative library design and screening have enabled the identification of membrane-active sequences with heretofore unknown properties, including clinically relevant, broad-spectrum activity against drug-resistant bacteria and enveloped viruses as well as pH-triggered macromolecular poration.

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