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Peptide-Mimetic Amphiphilic Polymers for Modulating Lipid Supramolecular Assemblies

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Abstract:

Lipid supramolecular assemblies, including biological membranes, are dynamic hierarchical structures that regulate molecular transport, signal transduction, and compartmentalization in living systems. In nature, membrane-active peptides and proteins modulate these assemblies through amphiphilic architectures realized by higher-order molecular frameworks such as α-helical motifs, in which hydrophilic and hydrophobic residues are spatially segregated to enable controlled membrane interactions. Inspired by these structural principles, we have developed peptide-mimetic amphiphilic polymers designed to interact with and modulate lipid supramolecular organization (**Figure**).

Our molecular design strategy is based on controlling the balance, distribution, and density of hydrophilic and hydrophobic side chains along synthetic polymer backbones. Although these polymers lack sequence-defined structures, their global amphiphilicity enables selective association with lipid assemblies and induces controlled structural transformations.

First, we present synthetic antimicrobial polymers that selectively target bacterial membranes. By tuning charge density and hydrophobic content, these polymers disrupt negatively charged bacterial membranes while minimizing toxicity toward mammalian cells, demonstrating potent antimicrobial activity. Mechanistic studies using model liposomes have clarified the polymer structure–dependent modes of action. [1)]

Next, we introduce amphiphilic polymers that spontaneously form lipid nanodiscs.[2)] Upon interaction with lipid membranes, these polymers solubilize bilayer fragments and stabilize discoidal assemblies without requiring protein scaffolds or detergents. The resulting nanodiscs function as efficient molecular carriers and provide a versatile platform for membrane engineering, including the evaluation of membrane-binding proteins.

These studies demonstrate how rational polymer design can emulate biological amphiphilic motifs to regulate lipid supramolecular assemblies and create bioactive functional materials.

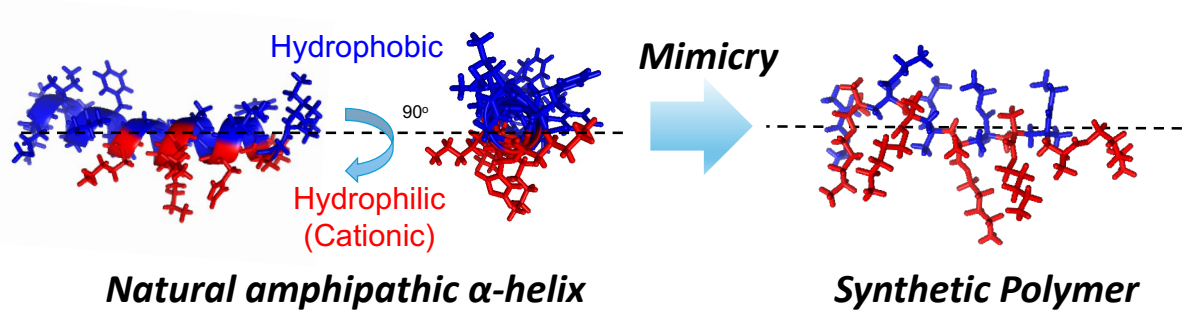

Figure *Peptide-mimetic design of membrane-active amphiphilic polymers*

References:

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2) K. Yasuhara, J. Arakida, T. Ravula, S. K. Ramadugu, B. Sahoo, J. Kikuchi, A. Ramamoorthy, *J. Am. Chem. Soc.* **2017**, *139*, 18657-18663.