Cell-Penetrating Peptidomimetics: Membrane Interaction and Intracellular Drug Delivery
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Purpose
1. To study the influence of physicochemical properties of different peptidomimetics on their membrane interaction and cellular uptake (CPP Characterization)
2. To investigate the potential of novel peptidomimetics as novel CPP for siRNA delivery (CPP Formulation)

Methods
1. Studies on CPP-Model Membrane: liposome/ lipid bilayer on silicon; Ellipsometry; Circular dichroism; Isothermal titration calorimetry; Molecular simulation; DLS; Cryo-TEM; SAXS.
2. Studies on CPP-cell culture:
   Preparation of an siRNA-loaded nanocarrier;
   Flow cytometry (cellular uptake & gene silencing activity); Confocal laser scanning microscopy; Cell viability assay.

Results
1. Results from CPP Characterization Part
   1a: The membrane and cellular activitives of different peptidomimetics are highly dependent on their physicochemical properties, where length, type of cationic side chains, side group chirality, terminal modification especially lipidization are of significant importance.
   1b: The overall correlation between cellular uptake and model membrane adsorption indicates that the initial interaction with the membrane is of key importance for the uptake for these peptidomimetics.
2. Results from CPP formulation Part
   2a: siRNA incorporated, lipo-α-peptide/β-peptoid modified, lipid-based nanocarriers can deliver siRNA into cells and induce gene silencing.
   2b: Cryo-TEM and SAXS showed the coexistence of lamellar (Lα) and inverse hexagonal (HII) phases, indicating that at least a part of the siRNA is located between the lipid bilayers.

Conclusion
1. Proof of concept that α-peptides/β-peptoid can be used as novel CPP for the intracellular delivery of siRNA
2. The close correlation between cellular uptake and model membrane adsorption, especially in the absence of lipidization, confirms that the initial interaction with the membrane is one of the key steps for the whole uptake process.