Design of Bioinspired Foldamer Architectures For Intracellular Delivery of Nucleic Acids

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One primary requirement for developing effective nucleic acid (NA) therapy systems to treat human diseases is the efficient delivery of the biomolecule to the target cells. Among the huge number of non-viral delivery systems reported so far, synthetic and natural cell penetrating peptides (CPPs) have recently emerged and present the advantage to be of limited and well-defined size, to be easily tailored by sequence manipulation and potentially less cytotoxic. LAH4 is a synthetic amphipathic cationic peptide that efficiently deliver plasmid DNA within the cell.[1] The particularity of this peptide is that it contains a His-rich sequence. It has been indeed demonstrated that due to its pH-responsiveness, the presence of several His residues in CPP sequences can overcome NA endosomal entrapment (proton-sponge effect). From a structural standpoint, this peptide has a strong propensity to fold into an α–helical conformation with all His residues located on one face of the helix.
Mimicking this peptide architecture with synthetic folded oligomers (*i.e.* **Foldamers**[2]) constitutes a valuable approach towards the design of original NA transport agents with improved transfection efficiency and enzymatic stability. However, despite significant advances in Foldamer chemistry, no investigation on their potential use to deliver cargo molecules within the cells has been reported so far.
Herein we will report the design of a potent pH-responsive bioreducible cell-penetrating foldamer (**CPF**) resulting from the dimerization of a small amphipathic oligourea sequence equipped with His-type units.[3] The capacity of this CPF to assemble with plasmid DNA (pDNA) to form **Foldaplexes** (by analogy to polyplexes) and to mediate its delivery will be discussed in details as well as its apparent non-cytotoxicity.

References.

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