Broadening the Landscape of Cyclodextrin-Based Vectors for Cell-Selective Nucleic Acid Delivery

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ABSTRACT

Lipid nanoparticles (LNPs) have emerged as a prominent non-viral delivery system for nucleic acids and have recently demonstrated their effectiveness in the development of mRNA-based COVID-19 vaccines. Nevertheless, LNPs face various challenges that impede their broader clinical adoption, encompassing issues related to stability, cargo size limitations, lack of cell specificity, and potential immunological side effects. The complex, multicomponent nature and polydisperse characteristics of LNPs, along with an incomplete understanding of the distribution of constituents within the nanoparticle structure, represent significant obstacles to optimization efforts. To overcome these limitations and advance nucleic acid therapies, it is imperative to explore innovative strategies centered on precision chemistry, molecular engineering, and novel design principles.

Previous research has indicated that carbohydrates, specifically cyclodextrins (CDs), offer promising avenues for addressing the above challenges.[1] The precision and accuracy of CD molecules in terms of composition, sequence, spatial relationships, and functionality make them an exceptional platform for investigating the interplay of diverse molecular parameters involved in the hierarchical assembly processes responsible for forming CD-nucleic acid nanocomplexes (CDplexes). Our previous investigations have unveiled how subtle modifications in the molecular architecture can lead to distinct assembly behaviors, resulting in diverse nanocomplex topologies with selective affinities for particular organs and cells.[2,3] Most reported examples typically exhibit a Janus-type architecture with separate cationic and lipophilic domains. In this study, we introduce a novel nucleic acid delivery prototype based on βCD, where the conventional orientation of hydrophilic and lipophilic components is intentionally disfavored due to geometric constraints, which we refer to as "geometrically frustrated amphiphiles" (GFAs). We will present the design, synthesis, and supramolecular properties of sequence-defined βCD-based cationizable GFAs. Computational simulations, including molecular mechanism and molecular dynamics (MM and MD), in conjunction with transmission electron microscopy (TEM), were employed to examine the preferred interaction modes and resulting arrangements. In vitro transfection experiments showcase the potential of βCD-based ionizable GFAs to surpass the conventional Janus archetype in encoding topological information, highlighting their applicability in the development of cell-selective nucleic acid therapeutics.

References

1. Ortiz Mellet, C.; García Fernández, J. M.; Benito, J. M. *Chem. Soc. Rev.* **2011**, *40*, 1586-1608.
2. Neva, T.; Carbajo-Gordillo, A. I.; Benito, J. M.; Lana, H.; et al. *Chem. Eur. J.* **2020**, *26*, 15259-15269.
3. Carbajo-Gordillo, A. I.; González-Cuesta, M.; Jiménez Blanco, J. L.; et al. *Chem. Eur. J.* **2021**, *27*, 9429-9438.