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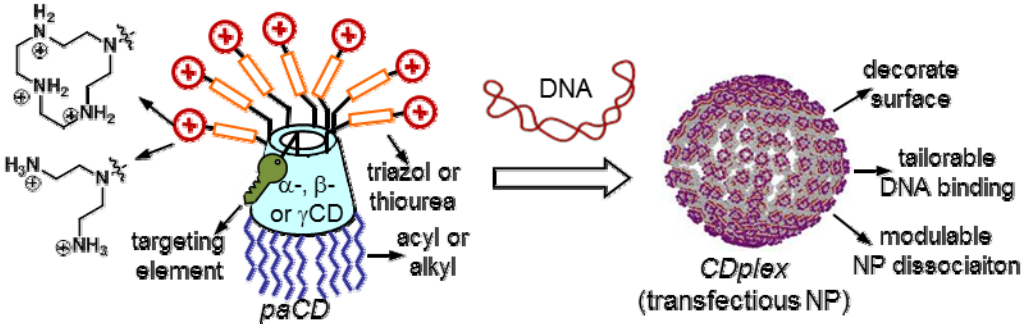
Tailoring self-assembling and targeting capabilities of CD-based nanoparticles for gene delivery

Juan M. Benito,[a] Iris Pflueger,[a] David Rodriguez-Lucena,[a] Carmen Ortiz Mellet[b] and José M. García Fernández[a]

a) Institute for Chemical Research, CSIC – Univ. Sevilla, Americo Vespucio 49, Sevilla E-41092, Spain; b) Department of Organic Chemistry, Faculty of Chemistry, Univ. Sevilla, Sevilla E-41012, Spain; e-mail: juanmab@iiq.csic.es

Nucleic acid-based drugs hold an unparalleled therapeutic potential due to their predictable and tailorable mode of action. Unfortunately, their bioavailability is poor and clinical application critically depends on the development of suitable delivery systems. Despite their innate capabilities for such task, the use of viral carriers is plagged of risks (e.g. immunogenicity or scaled-up production). Among artificial alternatives, cationic polymers and lipids hold a prominent position.[1] Aimed at merging the virtues of both, we conceived a new family of artificial gene vectors based on molecularly well-defined cyclodextrins (CDs) feturing segregated cationic and lipophilic domains (polycationic amphiphilic cyclodextrins, *paCDs*).[2] paCDs self-assemble in the presence of DNA to render tiny nanoparticles (*CDplexes*) exhibiting gene transfer capabilities that are intimately dependent on paCD molecular structure, eventually surpassing those of commercial standards (e.g. PEI).[3] Moreover, in contrast to most investigational artificial gene vectors, the flexibility of the synthetic scheme permits the modification of virtually any element on the CD scaffold with relative ease. Herein we wish to illustrate how this strategy can be implemented to (i) pinpoint the role of the hydrophilic/hydrophobic balance on paCD-DNA complex formation and dissociation, (ii) assess the influence of paCD cationic motifs on DNA binding, and (iii) decorate CDplex surface with specific binding epitopes (see figure). In the frame of a more ambitious project, aimed at devising targeted non-viral gene carriers, structural modifications will be correlated to gene transfer efficiency capabilities towards model cell lines.



[1] Mintzer, M.A.; Simanek, E.E. *Chem. Rev.* **2009**, *109*, 259.
[2] Ortiz Mellet, C.; Benito, J.M.; García Fernández, J. M. *Pure Appl. Chem.* **2013**, *85*, 1825 and references therein.
[3] Martínez, A.; Bienvenu, C.; Jiménez Blanco, J. L.; Vierling, P.; Ortiz Mellet, C.; García Fernández, J. M.; Di Giorgio, C. *J. Org. Chem.* **2013**, *78*, 8143 and references therein.