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Dynameric Frameworks for DNA Transfection

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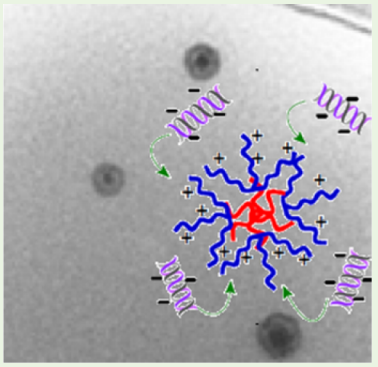
Supporting Information

ABSTRACT: The design of performant nonviral vectors for efficient cellular DNA uptake represents a grand challenge. The variability of DNA targets and of the transfected cells limits the discovery of highly active nonviral vectors. Dynamic constitutional strategy presented here, combining easy synthesis and rapid screening, enables the selection of dynameric frameworks, DFs, for DNA transfection. On the basis of reversible recombination of cationic heads and of hydrophilic/hydrophobic network-constitutive building blocks, the multivalent core−shell dendritic architectures with an optimal diameter of 100 nm may be adaptively generated in the presence of DNA targets. The fittest DFs simultaneously exhibit optimal DNA binding, superior transfection yield to standard transfection SuperFect agent and preserve high HEK 293T cell viability. The present results constitutes an important advancement toward novel biologically friendly, low-cost, and efficient nonviral vectors.



KEYWORDS: *dynamers, molecular recognition, DNA, cellular transfection*

Gene therapy is an innovative field, using DNA as drug to treat chronic diseases.[1−3] The transfer of DNA into the pathological cells is obtained by using vectors. Many nonviral molecular vectors, rationally designed to bind DNAs and transfer them into cell, show relative low efficiency compared to viral ones. To increase the transfection efficiency close to viral vectors, self-assembled nanostructures or nanomaterials (i.e., liposomes, polymerosomes, comblike or star-shaped dendrimers, etc.) have been rationally designed and tested.[4−6]

In contrast to the classical rational design methodology, dynamic constitutional approaches[7−9] allow for the generation of large dynamic combinatorial libraries-DCLs from small sets of building blocks. By virtue of the reversible interexchanges between the components, the DCLs can adapt to the external constraints, for example allowing selection events driven by a biotarget entity. Within this context, the DNA itself may be used as target to select an active system via recognition and self-assembly, directly from a library pool of components.[10] Extending the concept of DCLs to polymer/material science emerged dynamic polymers, dynamers:[11−13] materials that are linked through reversible connections and able to respond to internal or external factors by component exchange. The ability to adaptively implement spatial rearrangements of such reversible materials may induce a high level of correlativity of their 3D architectures and external surfaces in interaction with the DNA and the cell membrane barrier. In other words, this leaves the DNA to self-select and self-generate the fittest material, for its own compaction. Within this context, the use of dynameric materials for DNA transfection is an emerging field.[14,15] Herein, core-centers, hydrophobic/hydrophilic connectors, and positively charged molecular heads have been used to conceive 3D Dynameric Frameworks-DFs as innovative nanomaterials for DNA recognition and transfection. Depending on their variable composition and because of the reversible connectivity between DFs' constituents, they form modular networks/platforms that self-adapt to the DNA targets. Our strategy allowed rapid screening and easy and efficient identification of effective DFs of spherical morphology with high density charge for optimal DNA binding, good transfection efficiency, and good toleratance by human embryonic kidney 293T cells.

Dynamic Library Toolbox. Strategy. The DFs presented in this study involve the following components: (a) 1,3,5-benzenetrialdehyde **1** as a trifunctional core-center, able to cross-link network connectors and DNA-binding sites via the amino-carbonyl/imine reversible chemistry; (b) the bis-poly(propylene glycol), amine-terminated, ($M_n \approx 430$ g mol^{-1} Jeffamine-400 and $M_n \approx 2000$ g mol^{-1} Jeffamine-2000) **2** have been chosen as hydrophobic building blocks; they are known as low toxicity and high cellular DNA uptake systems;[16] (c) poly(ethylene glycol-3-aminopropyl) terminated; **PEG** seg-

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