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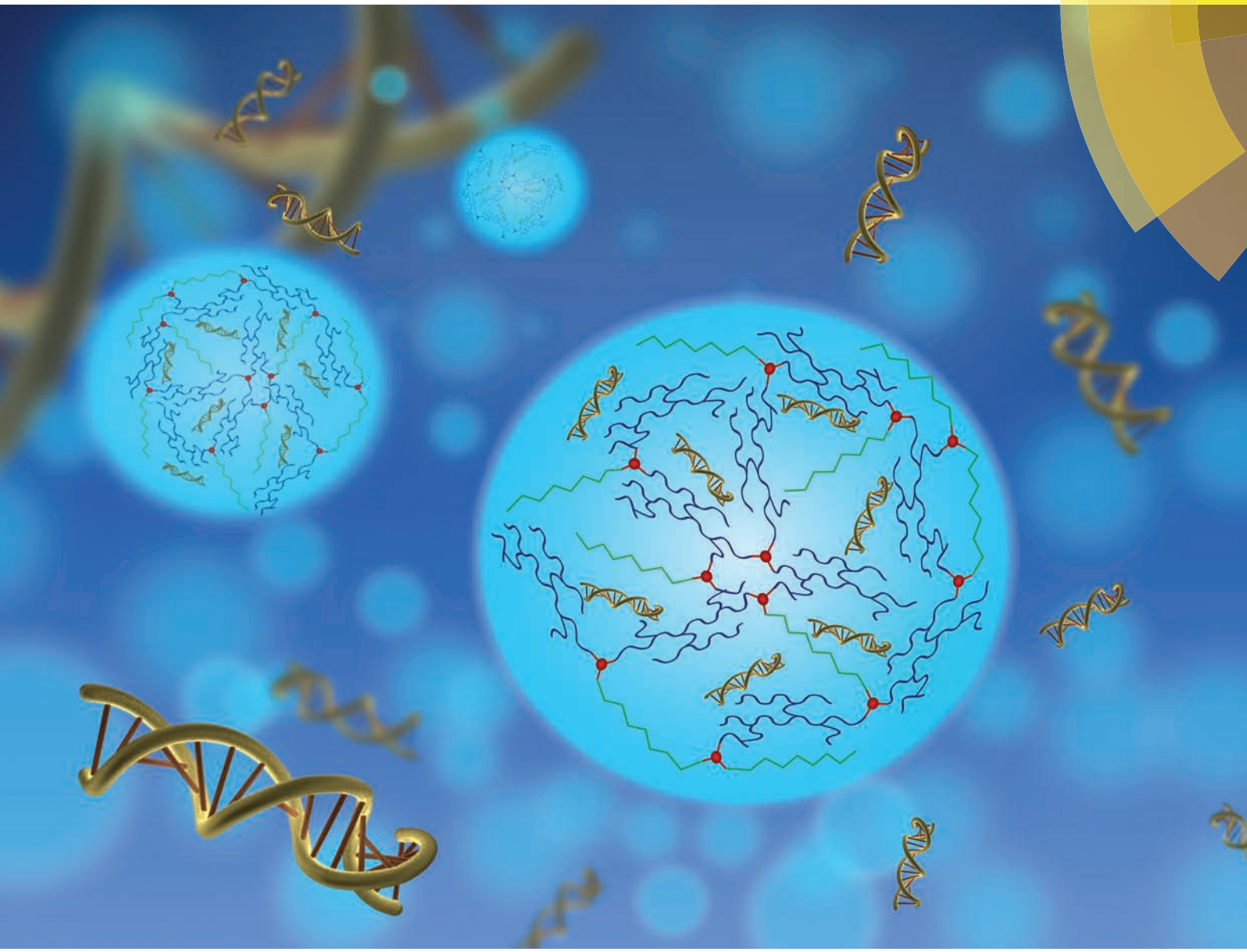

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# Dynamic constitutional frameworks (DCFs) as nanovectors for cellular delivery of DNA†

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We introduce Dynamic Constitutional Frameworks (DCFs), macromolecular structures that efficiently bind and transfect double stranded DNA. DCFs are easily synthesizable adaptive 3D networks consisting of core connection centres reversibly linked *via* labile imine bonds both to linear polyethyleneglycol (PEG, ~1500 Da) and to branched polyethyleneimine (bPEI, ~800 Da). DCFs bind linear and plasmid DNA, forming particulate polyplexes of 40–200 nm in diameter. The polyplexes are stable during gel electrophoresis, well tolerated by cells in culture, and exhibit significant transfection activity. We show that an optimal balance of PEG and bPEI components is important for building DCFs that are non-toxic and exhibit good cellular transfection activity. Our study demonstrates the versatility and effectiveness of DCFs as promising new vectors for DNA delivery.

## Introduction

Gene therapy promises to prevent, treat or cure disease by transferring with minimal side effects, therapeutic genetic material to specific cells or tissues, with the aid of either viral or non-viral vectors.[1,2] Despite their lower transfection efficiency compared to viral vectors, non-viral gene delivery systems have attracted a lot of attention[3] due to their unique advantages such as the ability to deliver single genes and lack of infectivity. Convergent strategies have been used for the design of multivalent molecular, supramolecular and nanometric non-viral vectors[4] mimicking natural delivery functions: membrane penetration, optimal DNA binding and packing, capacity for endosomal escape or nuclear localization, low cytotoxicity and anti-opsonisation functions.[5] However, due to the enormous variability of both DNA targets and nature of the transfected cells, rational design has been limited to the introduction of a reduced number of components and had to be accomplished by combinatorial approaches. In this context, the Dynamic Combinatorial Strategy proposed by Matile *et al.*[6] is one of the most attractive methods for rapid screening, allowing access to active systems from large and complex libraries. By virtue of reversible covalent exchanges between the hydrophilic heads and hydrophobic tails, the fittest *Dynamic molecular transfector* can adapt simultaneously to the DNA and the cell membrane barrier.

As for the design approaches, the dynamic constitutional strategy alternative may embody the flow of structural information from molecular to *Dynamic adaptive nanotransfectors*.[7] This concerns the use of linear Dynamic Polymers (Dynamers)[8,9] or of cross-linked Dynamic Constitutional Frameworks (DCFs).[7,10] These structures are composed of specific components and connector centres, linked together by labile, reversible covalent bonds. Importantly, they undergo exchange, incorporation/decorporation of their subunits, synergistically interacting and adapting the overall nanostructure in the presence of DNA and bilayered membrane components. This might play an important role in the ability to finely mutate and adaptively implement reversible rearrangements of the components toward a high level of correlativity of their hypersurfaces in interaction with the DNA and the cell membrane barrier. Thus, this strategy leaves the liberty to DNA systems to self-select and self-generate the carrier best adapted for its own transfection.

We have recently shown that linear PEG macromonomers, trialdehyde core connectors and positively charged guanidinium heads can be used to generate DCFs for DNA recognition.[7] The simplicity and robustness of the synthetic strategy allow rapid screening of conditions for generating systems with optimal DNA presenting/cell membrane synergistic affinities. Among potential components for the DNA recognition/transfection offered by the available toolbox, large libraries of active compounds may be used for these purposes.

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