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POLYMER ENGINEERING FOCUSING ON DRUG/GENE DELIVERY AND TISSUE ENGINEERING

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***Abstract*—Gene therapy represents a versatile approach for treating genetic disorders by manipulating cell functions. Research at the interface of biomaterials, gene therapy, and drug delivery has identified several design parameters for the non-viral vectors to perform optimum delivery of biologically active material into cells. Progress has been made towards achieving gene delivery, though the design principles for the materials and non-viral vectors that produce efficient delivery require further development. In this paper we summarize our contribution in design and preparation of efficient non-viral vectors by approaching two different strategies: preparation of core-like PEI-based structures and Dynamic Constitutional Frameworks as non-viral vectors. Our efforts resulted in yielding of architectures able to efficiently bind oligonucleotides of different length and even to transfect genetic materials into cells. Both strategies have a great potential in preparation of efficient and even selective gene carriers, and consistent work is being further carried out in our group.**

Keywords—gene therapy; non-viral vectors; polyethylenimine; dynamic constitutional frameworks.

I. INTRODUCTION TO GENE THERAPY

Gene therapy has gained significant attention over the past two decades as a potential method for treating genetic disorders such as severe combined immunodeficiency [1], cystic fibrosis [2], and Parkinson's disease [3], as well as an alternative method to traditional chemotherapy used in treating cancer [4]. Research efforts are currently focused on designing effective carrier vectors that compact and protect oligonucleotides for gene therapy: free oligonucleotides are rapidly degraded by serum nucleases in the blood when injected intravenously [5]. Initial research concentrated on using viral carriers, including both retroviruses and adenoviruses, as these vectors exhibited high efficiency at delivering both DNA and RNA to numerous cell lines [6]. However, fundamental problems associated with viral vector systems, including toxicity, immunogenicity, and limitations with respect to scale-up procedures, encouraged the investigation of other potential scaffolds to deliver exogenous DNA into targeted tissue [7]. Non-viral vector systems including cationic lipids, polymers, dendrimers and peptides offer potential routes for compacting DNA for systemic delivery. However, unlike viral analogues that have evolved possibilities to overcome cellular barriers and immune defense mechanisms, non-viral gene carriers consistently exhibit significantly reduced transfection efficiency as they are hindered by numerous extra- and intracellular obstacles. This drawbacks may be about to change owing to developments in material sciences, which have yielded new polymers, core molecules and functional building blocks as constituent parts of delivery vectors [8-12], as well as owing to the rapid progress of nanotechnology, which has enabled a better understanding of nano-sized materials for gene delivery [13,14]. In this article we summarize our advances in design, preparation and application of new non-viral gene delivery systems based on functionalized core molecules and branched polyethylenimine (bPEI). Additionally, we highlight our contribution in understanding the mechanism and particularities of the interaction between short nucleic acids and bPEI by means of molecular dynamic simulation [15].

II. CATIONIC POLYMERS FOR NUCLEIC ACIDS COMPLEXATION

Cationic polymers constitute an alternative class of non-viral DNA vectors and are partly attractive as a result of their immense chemical diversity and their potential for functionalization. Early examples of polymeric DNA vectors are poly(l-lysine) (PLL) and polyethylenimine (PEI). PEI and its variants are among the most studied polymeric materials for gene delivery. With a nitrogen atom at every third position along the polymer, PEI has a high charge density at reduced pH values. This attribute of PEI has been postulated to aid in condensation of oligonucleotides and endosomal escape [16]. The ability of PEI to promote gene transfection *in vitro* and *in vivo* was first demonstrated in 1995 [17]. Soon

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