scale manufacture [13, 21–23]. Nearly 26% of the total approaches used in clinical trials have been based on some kind of nonviral system [3]. It is clear, however, that despite the great potential of synthetic vectors, gene transfer is modest as compared to its viral counterparts [24, 25]. Of the developed nonviral gene-based therapeutics, the simplest approach involves vaccination using plasmid DNA (usually termed "naked DNA or pDNA") by subcutaneous or intramuscular injection [26–29]. It is important to point out that this approach is technically still considered within the nonviral gene-delivered approaches even though DNA is not bound to any compacting chemical carrier (e.g., cationic agents such as lipids or polymers). This technology is growing fast, and as of January 2014, around 782 completed or active phase I, II, and III studies were registered with the National Institute of Health (NIH, http://www.nih.gov, accessed 4 January 2014) for applications of a variety of diseases. Furthermore, as per gene therapy clinical trials using pDNA, ~17.8% (355 protocols) are currently under investigation worldwide [3]. Most of these studies include infectious and cancer-related diseases [30, 31]. Although the use of naked DNA has been associated with acceptable transfection and potent cellular and humoral immune responses as DNA vaccines [32–34], additional efforts have been recently dedicated to the optimization of specific viral vector-based DNA vaccines [28, 35] or in combination with cytokine adjuvants (e.g., granulocyte-macrophage colony-stimulating factor (GM-SCF) or interleukin-2 (IL-2) [30, 31]). Yet, no human vaccine has been approved by the Food and Drug Administration (FDA) or other regulatory agencies, the licensure of three distinct DNA vaccines for veterinary use (prophylactic West Nile virus vaccine for horses [36], prophylactic hematopoietic virus vaccine in salmonid fish [37], and a therapeutic DNA vaccine for melanoma in dogs [38]) has increased the enthusiasm in developing DNA vaccine technology as human therapeutic interventions. Due to physiological barriers, however, the naked DNA approach is not applicable for systemic gene delivery *in vivo* with the exception of hydrodynamic injections [39]. Hence, significant efforts have been directed toward developing efficient synthetic vectors for target cell delivery of nucleic acids (pDNA; small interfering RNA, siRNA; oligonucleotides; synthetic antisense molecules; among others) in animals and humans [40]. Cationic liposomes have been among the most studied and developed nonviral vectors since the pioneering publication of Felgner and collaborators showed that these positively charged drug vehicles are capable of mediating binding and delivery of DNA molecules to cultured cells [41]. Since this initial study, a considerable interest in exploiting liposomes as carriers of nucleic acids has led to the development of a number of cationic lipids (e.g., 1,2-dioleoyl-3-trimethylammonium-propane, DOTAP; 1,2-dimyristyloxypropyl-3-dimethyl-hydroxy ethyl ammonium bromide and cholesterol, DMRIE-C; 1,2-dioleyloxy-N,N-dimethyl-3-aminopropane, DODMA; 1,2-dilinoleyloxy-3-dimethylaminopropane, DLinDMA; among others) for both *in vitro* and *in vivo* gene transfer [40, 42–47]. Cationic lipids are considered the most efficient systems for nonviral gene delivery. Their relatively higher efficiency has been the result of the continuous development of new generations of cationic lipids that have been designed via chemical modifications to headgroup, hydrophobic domain and linker, and the development of better lipid compositions (i.e., lipid mixture or formulation). To date, approximately 5.5%