# The Sound of Silence. Computational/Experimental Investigations of Dendrimer-Based siRNA/DNA Delivery Systems

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Injected nano-scale drug delivery systems, or `nanovectors', are ideal candidates to provide breakthrough solutions to the time-honored problem of optimizing therapeutic index for a treatment. Even modest amounts of progress towards this goal have historically engendered substantial benefits across multiple fields of medicine, with the translability from, for example, a subfield of oncology to a field as distant as the treatment of infectious diseases being granted by the fact that the progresses had a single common denominator in the underlying technological platform. Transfection of cells with exogenous nucleic acids lies at the heart of molecular biology. It is a powerful technique that ultimately could be used therapeutically in humans, a goal that seems tantalizing just beyond the border of what modern medicine can do safely. The method depends on the efficient delivery of nucleic acid therapeutics (e.g., siRNAs) within a specific target cell population. Synthetic vector molecules comprise a valuable class of gene carriers that promise greater safety than viral vectors. Among these, linear and branched polymers, dendrons and dendrimers have been developed, tested and, ultimately, commercialized. Despite all research efforts devoted in this field, however, the efficiency of artificial vectors lags behind that of viruses. Some key biological steps have been identified, but still remain poorly understood and controlled. In particular, fewer studies have been devoted to the very first parameter: how do the nanocargos and nucleic acids interact? In this study, we combine simulation/experimental approaches to define the mode and the molecular requirements of the interaction of gene-based therapeutics and dendrimeric delivery agents. Information at the molecular level, which cannot be accessed with any other experimental techniques, can thus be obtained. These provides valuable information to devise optimal delivery systems that would increase the efficacy of gene therapy in cells and laboratory animals and move them toward clinical applications.