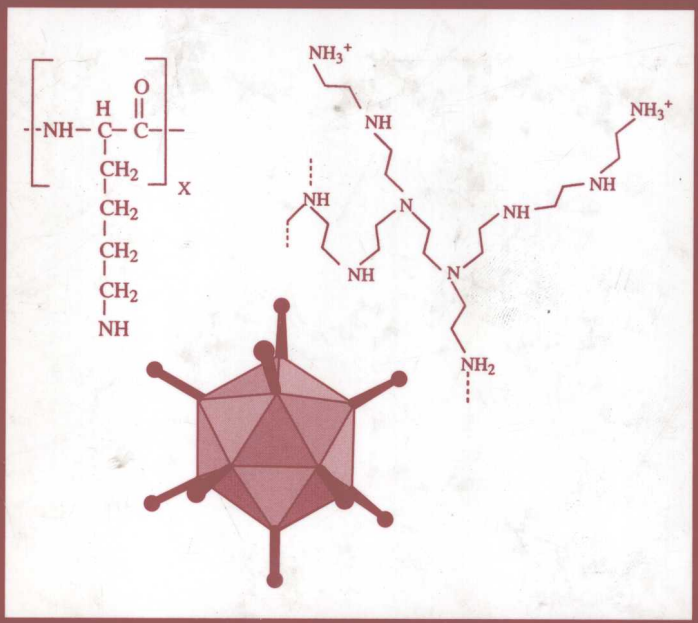
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 131

Pharmaceutical Gene Delivery Systems



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Pharmaceutical Gene Delivery Systems

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Preface

Gene therapy is a rapidly advancing field with great potential for the treatment of genetic and acquired systemic diseases. In developing pharmaceutical gene therapies, the disease, the therapeutic genes, and the gene delivery system need to be taken into consideration. The disease areas that have been most investigated in gene therapy to date are cancer and cardiovascular, pulmonary, and infectious diseases. Therapeutic genes for each of these diseases have been identified and are either in the clinic or due to enter the clinic. As future generation products are developed, the search for better therapeutic genes for the diseases currently being treated and genes to treat other diseases will continue. What remains to be identified is the gene delivery system needed to control the spatial and temporal modulation of the gene function. Furthermore, the duration, fidelity, regulation, and level of gene expression will be essential features to control by the design of specific gene expression systems.

Present delivery systems can be divided into virus-based, plasmid-based, and composites of both virus-based and plasmid-based systems.

Virus-based gene delivery systems comprise viruses that have been engineered not to replicate but to deliver genes to cells for expression. The viruses offer several advantages with regard to long-term expression, gene transfer efficiency, and expression of therapeutic genes. The limitations are (1) amenability of the viruses to pharmaceutical scale manufacture, (2) the restriction of viral infection to those cells expressing a receptor, and (3) the immunogenicity of the viral proteins. Viral systems do have applications for life-threatening diseases

that do not require large quantities of material to be administered. Preclinical research is focused on alleviating some of these limitations with adenovirus and adeno-associated virus being the lead candidates.

Plasmid-based gene delivery systems for so-called nonviral gene therapy are being developed as an alternative to the virus-based systems. Plasmid is propagated in and isolated from bacteria. The isolated plasmid by itself can be administered locally, yielding expression in the injected tissue. Formulating the plasmid with synthetic gene delivery systems can increase the transfection efficiency. These gene delivery systems comprise mainly lipids, peptides, or polymers. The delivery systems protect the plasmid from degrading enzymes prior to internalization, facilitate cellular uptake by endocytosis, and can promote endocytic vacuole release of the plasmid into the cytoplasm. Some of the technologies developed in the early stages of the field are presently used in the clinic. The technology is limited to local administration, yields transfection of a small portion of cells, and duration of expression is at best on the order of days to weeks. The disease indications (primarily cancer and cardiovascular and infectious diseases) to be treated by these technologies conform to these specifications.

This book is divided into the following sections: an introduction providing an overview of gene therapy, including a brief history summarizing the field of plasmid and virus-based gene delivery; a description of the present studies in the clinics covering the highlighted technology for each clinical application; a review of the plasmid-based expression systems; a summary of the present plasmid-based gene delivery technologies; the gene therapy applications, both preclinical and clinical; and new technologies for expansion of the applications to new diseases.

It is critical for the field of gene therapy to transition from a proof of concept to a pharmaceutical product at the beginning of the new millenium. A successful outcome will result in a new clinical modality that represents a revolutionary approach to medicine. One immediate benefit will be to produce a continuous level of therapeutic protein, avoiding the characteristic peak and trough behavior of intermittent administrations. Physicians will have the capability to turn genes on or off on demand, producing a therapy that can treat the disease rather than the symptoms and with minimal side effects.

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