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This is to acknowledge that the slide shown on the front cover of this journal was kindly supplied by Drs. Kai Ewert, Nelle L. Slack, Ayesha Ahmad, Heather M. Evans, Alison J. Lin, and Cyrus R. Safinya, Materials Department, Physics Department, and Biomolecular Science and Engineering Program, University of California, Santa Barbara, CA 93106-5121, USA and Dr. Charles E. Samuel, Molecular, Cellular, and Developmental Biology Department, and Biomolecular Science and Engineering Program, University of California, Santa Barbara, CA 93106-9610, USA. The cover slide shows the schematic sketches and electron micrograph images of synthetic vectors currently used in gene and drug delivery applications including clinical trials worldwide. Positive charged lipid–DNA complexes (middle) form a sandwich structure with DNA (genes) layered between membranes. Modern modeling methods predict that the sandwich structure is thermodynamically stable. Charge-neutral lipids can form spherical multilayered onion-like structures (top left) as vectors for short pieces of DNA. Spherical membranes containing drugs can be “double-bagged” inside of another outer layer of membrane creating a “Vesosome” vector (top right). Water-soluble polymers which spontaneously complex with DNA (bottom center) form a new class of lipid-less vectors.
Aims and Scope

*Current Medicinal Chemistry* aims to cover all the latest and outstanding developments in medicinal chemistry and rational drug design. Each bi-weekly issue contains a series of timely in-depth reviews written by leaders in the field covering a range of current topics in medicinal chemistry. *Current Medicinal Chemistry* is an essential journal for every medicinal chemist who wishes to be kept informed and up-to-date with the latest and most important developments.

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Preface

Gene carriers based on lipids or polymers or a combination of these - rather than on engineered viruses - are emerging as among the "hottest technologies" for delivering genes into cells for gene therapy and therapeutics. The topic has received increasing attention having been the subject matter of recent news features in highly visible technical Magazines such as Science and Chemical & Engineering News. Indeed, as described in Table I of the article by Ewert et al., nearly one quarter of ongoing gene therapy clinical trials are conducted with non-viral methods including lipids, polymers, and naked DNA. This thematic issue of Current Medicinal Chemistry is devoted to a series of reviews focusing on some of the latest findings in the area of synthetic non-viral gene delivery systems for therapeutic applications. A distinguishing feature of the articles is a significant emphasis on understanding vector-DNA complexes and their interactions with cells at the molecular level rather than in a purely empirical manner by trial and error.

The first article in this series by Ewert et al. describes the use of cationic lipids as gene vectors. The article describes how the use of modern technologies, including synthesis of tailored molecules and gene expression assays, synchrotron x-ray diffraction for structure determination, and three-dimensional laser-scanning confocal microscopy imaging of lipid-DNA interactions with cells, enables one to unravel structure-function relations with new insights for enhancing transfection efficacy.

To date, the main theoretical work on synthetic vectors has focused on cationic lipids complexed with DNA. The review by May and Ben-Shaul updates the reader on recent advances in modeling the structure and thermodynamic stability of cationic lipid-DNA complexes.

Although the majority of laboratories working on non-viral gene delivery systems focus on cationic lipids and polymers because of their natural ability to simultaneously condense therapeutic DNA and to attach to mammalian cells via their negative receptor molecules, the relative higher toxicity of the vectors compared to neutral lipid vectors has led some researchers to focus on other strategies. In their review Roux et al. describe a novel process by which DNA, a negative molecule, can be trapped between uncharged lipid membranes for delivery applications, even though the usual electrostatic attractions between DNA and lipid are absent.

Davis et al. introduce an entirely new class of novel water-soluble polymeric materials, cyclodextrin-containing polymers, which are shown to self assemble with DNA as a distinct type of polymer delivery technology. Their review outlines the effect of the molecular structure and the role of hydrophobic and hydrophilic interactions as well as chemical modifications of the end groups and the backbone on the activity of these molecules as drug carriers.

The final review by Kisak et al. describes the invention of the vesosome, a synthetic carrier consisting of a set of vesicles contained within an outer lipid membrane. The remarkable structure of the vesosome, which is reminiscent of the eukaryotic cell with inner organelles, allows one to compartmentalize for simultaneous delivery of different drug molecules for a range of functions.

The ultimate goal of research and development on virus-free carriers is to develop a science base, which will lead to the design and synthesis of optimal carriers of DNA for gene therapy and disease control. On a final note, it should be mentioned that the recent renaissance in the field is also partly because of the realization of the potential of the delivery technology in transferring large pieces of DNA, such as sections containing over a million base pairs, into cells. Thus, one may envision future applications with synthetic-vectors designed to deliver a cassette of human genes together with their regulatory sequences. Such a feat is simply not in the realm of possibilities with current viral vector strategies.

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