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Preface

Engineered polymers and polymeric systems in controlled drug delivery and targeting

Successful pharmacotherapy intervention requires strict control over the spatial and temporal characteristics of drug delivery. This could only be achieved through the development of well-designed drug carriers that would be able to meet the specific delivery challenges that each particular disease poses, and to overcome the physiological barriers (extra- and intra-cellular degradation, unfavorable tissue distribution and poor penetration through cell membranes), preventing the drug molecules to reach the intra-cellular sites of action at the required quantities and for the required period of time. Such well-designed carriers are particularly important for the delivery of nucleic-acid-based "drugs", which cannot effectively be delivered with conventional delivery systems. Indeed, one of the greatest contemporary challenges to drug delivery science is to improve the efficiency of 'non-viral' gene delivery, which despite the progress that has been made in the recent years is still inefficient. Engineered polymers are the materials used today to construct carriers with controlled drug delivery properties, that is, carriers which could perform one or more of the following: (a) increase drug availability to the target cells, (b) increase selectivity towards the target cells, (c) release their drug load only at the site of drug action (or nearby) in response to internal or external stimuli (e.g. pH or temperature changes) and (d) release drug only when it is required in response to biological signals (e.g. an increase in glucose levels in blood). Engineered polymers and polymeric delivery systems are the subject of the review articles compiled in this special issue.

"Targetability" is an important attribute for drug delivery systems in the case of drugs of low selectivity, such as anticancer drugs. Targeted drug carriers can increase the fraction of drug dose reaching the target cells (e.g. tumor cells), thereby increasing efficacy and reducing toxicity. In the first paper, H. Maeda et al. discuss how the polymeric drugs can have an increased accumulation to tumor site relatively to the parent (non-polymer-conjugated) drugs based on the enhanced permeability and retention (EPR) effect. They also describe the pathophysiological factors involved in the generation of this effect, and suggest methods of EPR effect augmentation, for example, by angiotensin II-induced hypertension. Finally, they analyze the advantages that polymeric drugs may have been compared to the free drugs, which include the tumoritropic and lymphotropic nature of the polymeric drugs, the decrease of drug side effects and the possibility of overcoming multidrug resistance.

The controlled drug delivery systems currently under development are based on polymers with tailor-made properties for the intended application. In the second paper of this issue, S. Kim et al. provide an overview of the structural characteristics, properties and possible applications of "smart" (stimuli-responsive) polymers and the strategies to develop targeted drug delivery systems. They also comment on "parallel synthesis", which has been introduced recently as a tool for the fast development of new polymeric biomaterials. Despite the intensive research in the recent years, few controlled drug delivery systems have made it to the marketplace. The main reason for this poor success rate could be that important factors such as safety/biocompatibility, scalability and cost/benefit balance of the new controlled drug delivery systems are often overlooked during the development phase. S. Kim et al. comment briefly on these issues, and conclude that the study to develop new and more efficient drug delivery systems should be accompanied by an effort to make them safe and "massively producible". In the third paper, V. Torchillin reviews the current status of the newest generation of drug carriers, which is represented by the "multifunctional" drug carriers. These carriers are liposomes, micelles and polymeric nanoparticles that combine several desirable properties such as blood longevity (long circulation), targetability, intra-cellular penetration and stimuli sensitivity. Such drug delivery systems "could eventually allow for combined therapeutic and diagnostic systems with dramatically enhanced efficacy".

Dendrimers (from the Greek word "dendron" meaning "tree") are unique among nanoparticulate drug carriers in the sense that they can be synthesized in a layer-by-layer fashion to produce branched nanostructures of precise architecture. In the forth paper, S. Svenson discusses the biocompatibility of dendrimers and reviews their application in controlled drug delivery. The advances in block copolymer chemistry has allowed for the development of amphiphilic block copolymers, which can form in aqueous systems unilamellar vesicles called "polymersomes". These vesicles can encapsulate both hydrophilic and hydrophobic drugs. Since, unlike polymeric nanoparticles, polymersomes are formed under mild conditions (i.e. without the application of intense shear forces and in the absence of organic solvents), they may prove particularly useful as the carriers of biomacromolecules (e.g. proteins), which are unstable under intense shear forces or in the presence of organic solvents. In the fifth paper, D.A. Christian et al. review the recent progress in this field, which has led to the development of polymersome carriers with controlled drug delivery properties.

Gene therapy has been considered for the treatment not only of hereditary disorders and cancer but also for the treatment of cardiovascular diseases, age-related degenerative diseases, wound healing and tissue engineering. Replication-deficient viruses have been used for gene delivery because of their high transfection efficiency. However, the risks associated with their use (insertional mutagenesis and unwanted immune responses) have made necessary the search for alternative safer gene delivery systems. This resulted to the development of synthetic gene carriers based on

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cationic lipids (“lipoplexes”) or cationic polymers (“polyplexes”). In order to design effective DNA delivery systems we should “learn from nature”, and K. Itaka and K. Kataoka highlight the approaches that are currently being taken to improve the non-viral gene delivery systems so that they better replicate the structures and mechanisms of natural viruses, which are the most efficient gene delivery systems. They also discuss their own approach for gene delivery involving polyplex micelles composed of poly(ethyleneglycol)-block-polycations. The recent data indicate that mRNA delivery to cells is much more effective than the delivery of pDNA, presumably because mRNA does not have to be transported into the nucleus. Since there is no risk of integration into genomic DNA, the use of mRNA-based gene transfer appears to be a promising new strategy for the treatment of inherited and acquired diseases. A. Yamamoto et al. review the mRNA delivery systems and comment on the future directions of mRNA-based gene therapy and vaccination. RNA interference is the down-regulation of genes at the post-transcriptional level using small nucleic acids, such as small interfering RNA (siRNA) and antisense oligodeoxynucleotides (ODNs). The recent advances in polymer chemistry have allowed for the development of polymer nanocarriers, which are able to efficiently deliver RNA interference agents in vivo. These nanocarriers are the subject of the review by H. de Martimprey et al.

Mucoadhesion could be defined as the attachment of polymers to a mucosal surface. Polymers with mucoadhesive properties have been used to extend the residence of drug delivery systems to mucus surfaces in the body with the aim either to prolong the local drug effect or to increase the systemic drug availability. G.P. Andrews et al. discuss the theories which have been presented to explain the mechanisms involved in mucoadhesion, and review the progress that has been made in the design of mucoadhesive polymers and systems from the first-generation charged hydrophilic polymers to the second-generation engineered systems based on lectin, thiol and other functional groups. In their paper, L. Serra et al. provide a critical analysis of the chain dynamics responsible for the action of mucoadhesive biomaterials, and discuss the recent research that is focused on the development of “adhesion promoters” in order to increase the adhesion between polymers and mucus.

I would like to thank all the authors for their excellent contributions to this special issue dedicated to engineered polymers and polymeric systems in controlled drug delivery and targeting. I am confident that the articles of this issue provide the researchers in the field with the state of the art in the polymers and systems design, and will stimulate further research towards the development of drug delivery systems which will meet the drug delivery needs of today.

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