
Preface

Advances in understanding the molecular mechanisms of disease together with the advent of recombinant DNA and other technologies have opened opportunities for a vast array of novel therapeutic biopharmaceuticals and diagnostic agents. However, even natural biomolecules present a myriad of problems that limit their potential as pharmaceutical agents. Rapid degradation and elimination, immunological reactions, and toxicity are often associated with new biopharmaceuticals, much as with conventional agents.

Targeted delivery systems have the potential to increase the efficacy of existing diagnostic and therapeutic agents and also create an opportunity for the use of new pharmaceuticals, substances that themselves can be harmful to normal tissues. Both passive and active targeting have been exploited. Most active targeting strategies have focused on antibody conjugates since preparation of highly specific monoclonal antibodies is well established. However, a new wave of conjugates exploiting other ligands is underway. Access to the target tissue remains an obstacle and is an area where passive targeting can be useful.

In *Drug Targeting: Strategies, Principles, and Applications* we have tried to compile a state-of-the-art volume on current targeting approaches. The first section focuses on certain key strategies applied to date, and how to build the antibody–ligand constructs. This is followed by a section on theoretical considerations for targeting, focusing on approaches relevant to solid tumors. The last section deals with some experimental and clinical applications of targeted drug delivery systems.

Immunotoxins—constructs comprising an antibody to target the appropriate cell tissue or organ and a toxin—were among the first targeted molecules. Chemical construction of immunotoxins is extensively addressed by Ghetie and Vitetta. Ribonuclease-antibody chimeras—a new type of immunotoxin, based on human and humanized ribonuclease proteins that are known to have host–defense activities and expected to be less toxic and less immunogenic than immunotoxins based on plant and bacterial toxins—are discussed by Newton and Rybak in two chapters, one detailing a chemical approach to their synthesis and the second dealing with the preparation of fusion proteins. The production of fusion toxins is also addressed by Pastan.

Raso presents an elegant targeting approach exploiting bispecific antibodies. One antibody binds the effector molecule reversibly, while the second antibody targets the complex to selected sites on the cell membrane. No covalent or chemical

modification of the bioactive molecule is required and thus its structural integrity and full biologic potential are preserved. The properties of enzyme–antibody conjugates are discussed by Muzykantov using an approach based on streptavidin–biotin linkers. Chapters by Cullis et al., Torchilin, and Agrawal disclose strategies for targeting liposomes to tissues other than those of the reticuloendothelial system. The most widely used ligands are again antibodies, but such molecules as oligosaccharides, peptides, other proteins, and vitamins have also been employed.

Lee and Low give details on the preparation of folate-bearing conjugates targeted to tumors with folate receptors. Folate has been used in the targeted delivery of proteins, liposomes, gamma imaging agents, oligodeoxyribonucleotides, and gene transfer vectors. Low immunogenicity, rapid extravasation, tumor permeation, and systemic clearance, together with resistance to denaturation, are some of the advantages of folate over the antibody targeting.

Finally, classic targeting methodologies are now being adapted for targeted gene transfer. Pincus discusses the preparation of antibody–virus conjugates to target viruses to the receptor cells. Details of current methods applied to lipid-based plasmid delivery systems are dealt with by Wasan et al.

On the applications of these targeted vehicles, Torchilin deals extensively with targeting myocardial infarction using liposomal systems. Agrawal and Pincus describe the importance of using monoclonal antibodies raised against infected cells to target malaria and HIV-infected cells, respectively. The fusion proteins prepared by Pastan are targeted to leukemia and lymphoma and the pulmonary endothelium is targeted by the antioxidant enzyme–antibody conjugates prepared by Muzykantov.

Targeting of tumors has received the most attention and therefore three chapters giving theoretical aspects have been included. Thomas gives details of both passive and active targeting to tumors. Ching deals with targeting tumor blood flow as a more universal approach for tumor treatment either singly (by generation of hypoxia) or in combination with other therapies (by entrapment of other drugs within the tumor site, including cytotoxic and “bio-reductive” drugs that are activated selectively by metabolic reduction under hypoxic conditions).

Drug Targeting: Strategies, Principles, and Applications does not, of course, cover every class of drug and biopharmaceutical targeting to many tissues and diseases. We have tried to include illustrative and interesting examples of the more classical targeting approaches and of the new wave of very promising ligands and constructs, all of which are opening new horizons for targeted drug delivery.

Finally, the editors are grateful to the contributors for the patience and perseverance required to complete this volume.

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<http://www.springer.com/978-0-89603-531-7>

Drug Targeting
Strategies, Principles, and Applications
Francis, G.E. (Ed.)
2000, X, 318 p., Hardcover
ISBN: 978-0-89603-531-7
A product of Humana Press