

PREFACE

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"In medicinal chemistry, the ruling principle is: *Corpora non agunt nisi fixate*, meaning that active substances are only effective if they have a specific affinity for their target"

Paul Ehrlich, 1913, in *Chemotherapy*

Medicinal active agents, whose effects are based on the universal concept of "target recognition". Their history is characterized by a limited number of revolutionary advances. Except for the traditional medicines derived from the serendipity-driven use of natural plant decoctions, such conceptual revolutions or "quantum leaps" in drug discovery have always resulted from scientific advances. The first revolution resulted from progresses in both analytical and synthetic chemistry, together with the Paul Ehrlich "magic bullet" concept. This has been at the basis of the discovery of chemical drugs directed to a molecularly defined "receptor" target. Indeed, before the 1913 Paul Ehrlich "lock and key" chemotherapy theory, the concept, today widely accepted, that molecular receptors in living organisms can be selectively affected by chemical compounds was hardly conceivable.

Biochemistry breakthroughs and the advances in both protein characterization and recombinant DNA technology paved the way to the use of proteins as therapeutic agents. Today, recombinant cytokines and hormones, such as erythropoietin (EPO), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon, and monoclonal antibodies represent a considerable achievement and leading field of drug discovery.

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As an overwhelming rule for both chemical and protein drugs the molecular target in the patient is a protein, with rare exceptions including cytotoxic anticancer agents such as cisplatin which bind to DNA independently of the genetic sequence.

Representing the most recent revolutionary leap forward, both *genetic pharmacology* and *gene therapy* are based on the use of the genetic code. Genetic pharmacology represents the critical ultimate step of the Paul Ehrlich "lock and key" concept, in which the drug target is an intracellular genetic sequence within either a DNA or a RNA molecule which is recognized by Watson-Crick or Hogsteen base pairing. By contrast, in gene therapy a gene is administered to the patient's cells, leading to the transcription by RNA polymerases of a RNA, which can be by itself a therapeutic agent, or most often represents an mRNA translated into a therapeutic protein by the ribosome machinery. In gene therapy, the administered gene can thus be considered as a "prodrug", with the amplification advantage resulting from the continuous intracellular production of the therapeutic RNA and eventually protein.

This textbook describes the concepts and applications of genetic pharmacology and gene therapy. Extensive biological, pharmaceutical and medicinal aspects are presented in a very simple and pedagogical way by world-recognized experts. This rapidly developing field is finely introduced by Professor Thierry VandenDriessche, former President of the European Society of Gene & Cell Therapy. The basic definitions and principles are presented in Part I, while the various vectors and gene-delivery techniques are introduced in Part II. Examples of therapeutic applications are described in Part III, and a more technological Part IV is dedicated to vector production.

In addition to chapters written in a pedagogical "textbook style" advising the reader on a few key reviews for further reading, several chapters have been written as reviews including an extensive bibliography. Therefore, both newcomers and experienced readers might find in the present textbook the most helpful introductory information or more specialized answers to their specific needs.

I am honored and grateful that such an assembly of talents has accepted the invitation to contribute to this textbook, which I hope will prove most useful to biological and medicinal students and scientists planning to use gene delivery for basic science or translational medical application, and to medical doctors wishing to be introduced to the exciting new frontline medical fields of genetic pharmacology and gene therapy.

Professor Daniel Scherman