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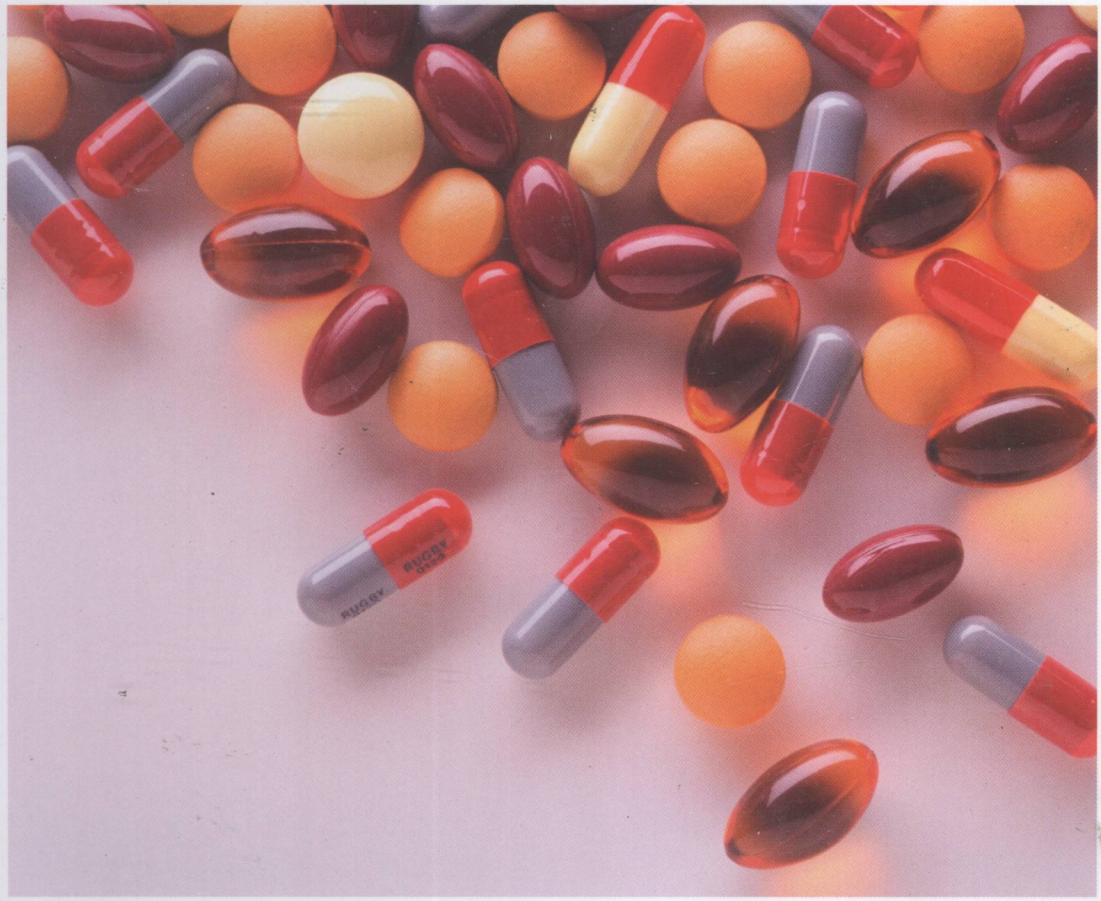
Pharmacology

From Drug Development to Gene Therapy

Volume 2



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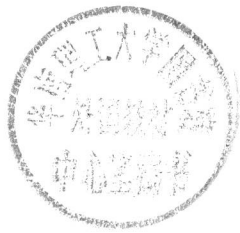

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Robert A. Meyers

Related Titles

Meyers, R. A. (ed.)

Encyclopedia of Molecular Cell Biology and Molecular Medicine

16 Volume Set

2005

ISBN: 978-3-527-30542-1

Kayser, O., Müller, R. H. (eds.)

Pharmaceutical Biotechnology

Drug Discovery and Clinical Applications

2004

ISBN: 978-3-527-30554-4

Knäblein, J. (ed.)

Modern Biopharmaceuticals

Design, Development and Optimization

2005

ISBN: 978-3-527-31184-2

Preface

This treatise on pharmacology was compiled from a selection of key articles from the recently published 16 volume *Encyclopedia of Molecular Cell Biology and Molecular Medicine* (ISBN 978-3-527-30542-1, http://www.meyers-emcbmm.de/). This two volume publication is composed of 33 detailed articles arranged in four sections covering Drug Development; Innovative Therapeutic Approaches; Cancer Therapeutics; and Gene Therapy. The articles were prepared by eminent researchers from many of the major molecular biology and pharmacology research institutions spanning the globe.

Leading participating academic institutions include: the University of California, San Francisco; the University of Michigan, Ann Arbor; the University of California, Los Angeles; the University of Southern California; the Mayo Clinic; the Massachusetts Institute of Technology; the Dana-Farber Cancer Institute; Harvard Medical School; the Baylor College of Medicine; the University of Florida, Gainesville; the Welsh School of Pharmacy, Cardiff University; the University of Queensland, Brisbane, Australia; the University of Strathclyde, Glasgow, Scotland; the Paul-Ehrlich-Institut, Langen, Germany; the Robert Koch-Institut, Berlin; Germany; the University of Tübingen, Tübingen, Germany; University of Ulm, Ulm, Germany; the University of Lübeck, Lübeck, Germany; University of Glasgow, Glasgow, UK; Université Libre de Bruxelles, Brussels, Belgium; Pharmaceutical Biology, Rijksuniversiteit Groningen, Groningen, The Netherlands; the Technion-Israel Institute of Technology, Haifa, Israel; the Indian Institute of Chemical Technology, Hyderabad, India; and the Hospital General of Granollers, Barcelona, Spain.

The research groups of major pharmaceutical firms also participated including: Novartis Pharma Research Centre, Horsham, UK; Schering AG, Berlin, Germany; GlaxoSmithKline Pharmaceutical Research & Development, Collegeville, PA; Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA; as well as ARIAD Pharmaceuticals, Cambridge, MA and Exelixis, South San Francisco.

Each article begins with a concise definition of the subject and its importance, followed by the body of the article and extensive references for further reading. The references are divided into secondary references (books and review articles) and primary research papers. Each subject is presented on a first-principle basis, including detailed figures,

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tables and drawings. Because of the self-contained nature of each article, some overlap among articles on related topics occurs. Extensive cross-referencing is provided to help the reader expand his or her range of inquiry.

The master publication, which is the basis of the Pharmacology set, is the *Encyclopedia of Molecular Cell Biology and Molecular Medicine*, which is the successor and second edition of the VCH *Encyclopedia of Molecular Biology and Molecular Medicine*, and covers the molecular and cellular basis of life at a university and professional researcher level. The first edition, published in 1996–1997 was utilized in libraries around the world. This second edition is double the first edition in length and comprises the most detailed treatment of both molecular and cell biology available today. The Board with twelve Nobel laureates and I believe that there is a serious need for this publication, even in view of the vast amount of information available on the World Wide Web and in text books and monographs. We feel that there is no substitute for our tightly organized and integrated approach to selection of articles and authors and implementation of peer review standards for providing an authoritative single-source reference for undergraduate and graduate students, faculty, librarians and researchers in industry and government.

Our purpose is to provide a comprehensive foundation for the expanding number of molecular biologists, cell biologists, pharmacologists, biophysicists, biotechnologists, biochemists and physicians as well as for those entering the field of molecular cell biology and molecular medicine from majors or careers in physics, chemistry, mathematics, computer science and engineering. For example, there is an unprecedented demand for physicists, chemists and computer scientists who will work with biologists to define the genome, proteome and interactome through experimental and computational biology.

The Board and I first divided all of molecular cell biology and molecular medicine into primary topical categories and each of these was further defined into subtopics. The following is a summary of the topics and subtopics:

- Nucleic Acids: amplification, disease genetics overview, DNA structure, evolution, general genetics, nucleic acid processes, oligonucleotides, RNA structure, RNA replication and transcription.
- Structure Determination Technologies Applicable to Biomolecules: chromatography, labeling, large structures, mapping, mass spectrometry, microscopy, magnetic resonance, sequencing, spectroscopy, x-ray diffraction.
- Proteins, Peptides and Amino Acids: analysis, enzymes, folding, mechanisms, modeling, peptides, structural genomics (proteomics), structure, types.
- Biomolecular Interactions: cell properties, charge transfer, immunology, recognition, senses.
- Molecular Cell Biology of Specific Organisms: algae, amoeba, birds, fish, insects, mammals, microbes, nematodes, parasites, plants, viruses, yeasts.
- Molecular Cell Biology of Specific Organs or Systems: excretory, lymphatic, muscular, neurobiology, reproductive, skin.
- Molecular Cell Biology of Specific Diseases: cancer, circulatory, endocrine, environmental stress, immune, infectious diseases, neurological, radiation.
- Biotechnology: applications, diagnostics, gene altered animals, bacteria and fungi, laboratory techniques, legal, materials, process engineering, nanotechnology, production of classes or specific molecules, sensors, vaccine production.

- Biochemistry: carbohydrates, chirality, energetics, enzymes, biochemical genetics, inorganics, lipids, mechanisms, metabolism, neurology, vitamins.
- Pharmacology: chemistry, disease therapy, gene therapy, general molecular medicine, synthesis, toxicology.
- Cellular Biology: developmental cell biology, diseases, dynamics, fertilization, immunology, organelles and structures, senses, structural biology, techniques.

We then selected some 340 article titles and author or author teams to cover the above topics. Each article is designed as a self-contained treatment. Each article begins with a key word section, including definitions, to assist the scientist or student who is unfamiliar with the specific subject area. The encyclopedia includes more than 3000 key words, each defined within the context of the particular scientific field covered by the article. In addition to these definitions, the glossary of basic terms found at the back of each volume, defines the most commonly used terms in molecular and cell biology. These definitions should allow most readers to understand articles in the encyclopedia without referring to a dictionary, textbook or other reference work.

Larkspur, March 2008

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Editor-in-Chief

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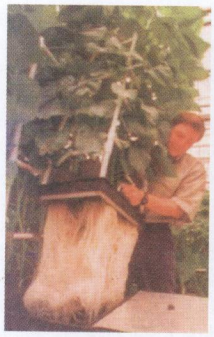
Color Plates

Phytomedics (tobacco):

- Root secretion, easy recovery
- Greenhouse contained tanks
- High density tissue
- Salts and water only
- Tobacco is well characterized
- Stable genetic system



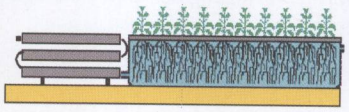


Fig. 6 (p. 455) Secretion of the biopharmaceuticals via tobacco roots. The tobacco plants are genetically modified in such a way that the protein is secreted via the roots into the medium ("rhizosecretion"). In this example, the tobacco plant takes up nutrients and water from the medium and releases GFP (Green Fluorescent Protein). Examination of root cultivation medium by its exposure to near ultraviolet-illumination reveals the bright green-blue fluorescence characteristics of GFP in the hydroponic medium (left flask in panel lower left edge). The picture also shows a schematic drawing of the hydroponic tank, as well as tobacco plants at different growth stages, for example, callus, fully grown, and greenhouse plantation. Source: Knäblein J. (2003) *Biotech: A New Era in the New Millennium – Biopharmaceutic Drugs Manufactured in Novel Expression Systems*, DECHEMA-Jahrestagung der Biotechnologen, Munich, Germany, 21.

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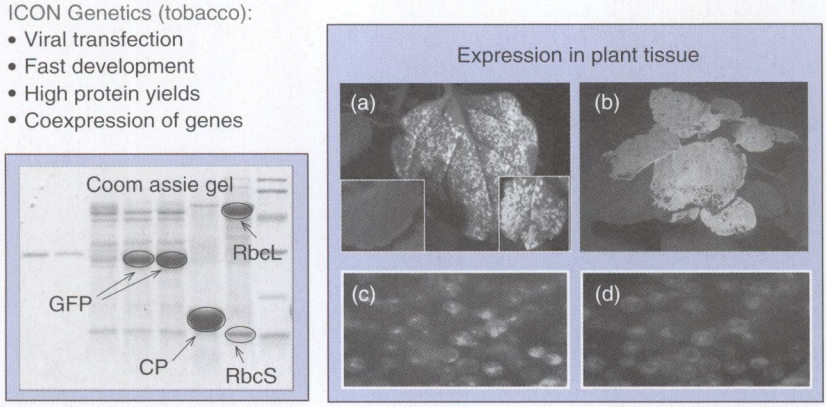

Fig. 7 (p. 456) Viral transfection of tobacco plants. This new generation platform for fast (1 to 2 weeks), high-yield (up to 5 g kg^{-1} fresh leaf weight) production of biopharmaceuticals is based on proviral gene amplification in a nonfood host. Antibodies, antigens, interferons, hormones, and enzymes could successfully be expressed with this system. The picture shows development of initial symptoms on a tobacco following the Agrobacterium-mediated infection with viral vector components that contain a GFP gene (a); this development eventually leads to a systemic spread of the virus, literally converting the plant into a sack full of protein of interest within two weeks (b). The system allows to coexpress two proteins in the same cell, a feature that allows expression of complex proteins such as full-length monoclonal antibodies. Panels (c) and (d) show the same microscope section with the same cells, expressing Green Fluorescent Protein (c) and Red Fluorescent Protein (d) at the same time. The yield and total protein concentration achievable are illustrated by a Coomassie gel with proteins in the system: GFP (protein of interest), CP (coat protein from wild-type virus), RbcS and RbcL (small and large subunit of ribulose-1,5-bisphosphate carboxylase). Source: Knäblein J. (2003) *Biotech: A New Era in the New Millennium – Biopharmaceutic Drugs Manufactured in Novel Expression Systems*, DECHEMA-Jahrestagung der Biotechnologen, Munich, Germany, 21.

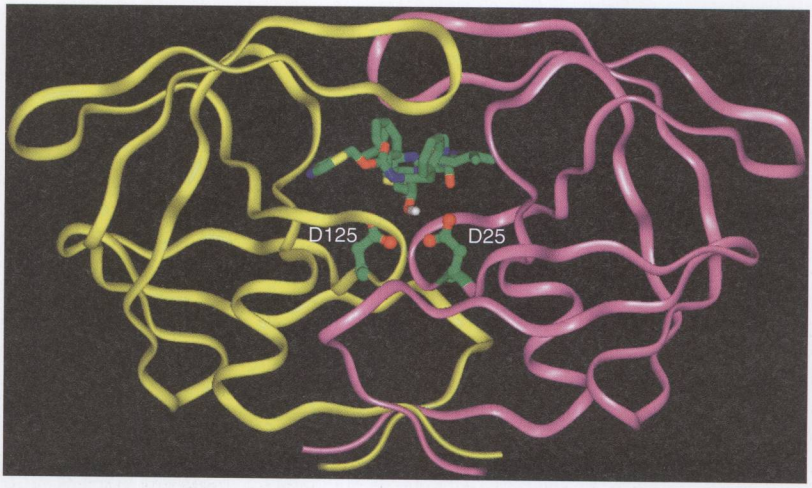

Fig. 5 (p. 564) Crystal structure of HIV-1 protease (PR) complexed with ritonavir (PDB1HXW). The two monomers of the PR are represented as ribbon models (yellow and magenta). The two catalytic aspartate residues (D25 and D125) are rendered as ball and stick models while the ritonavir is represented by a stick model. The hydroxyl group of the ritonavir occupies the space between two aspartate residues.

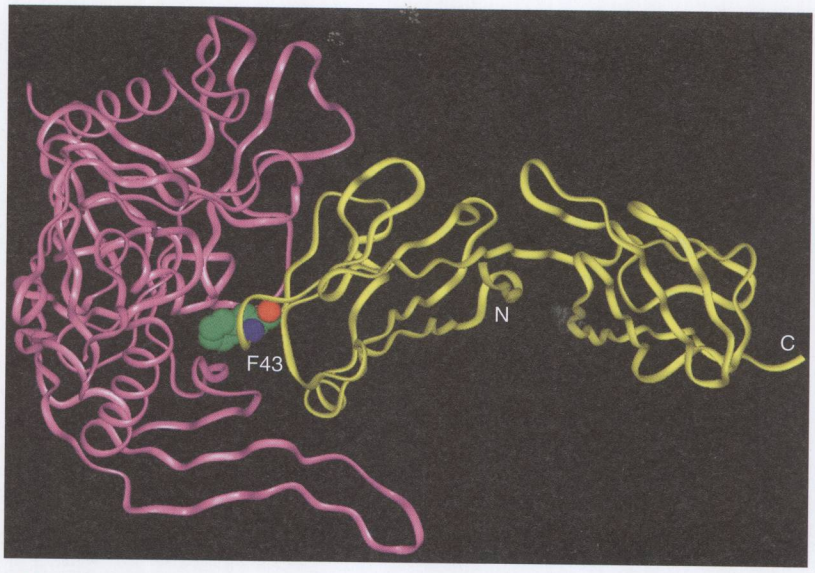

Fig. 8 (p. 569) The ribbon diagram of crystal structure shows binding of gp120 (magenta) to CD4 receptor (yellow). The F43 (shown as CPK model) of CD4 protrudes into a hydrophobic cavity on gp120. In this orientation, the CD4 binding cavity on gp120 is clearly visible.

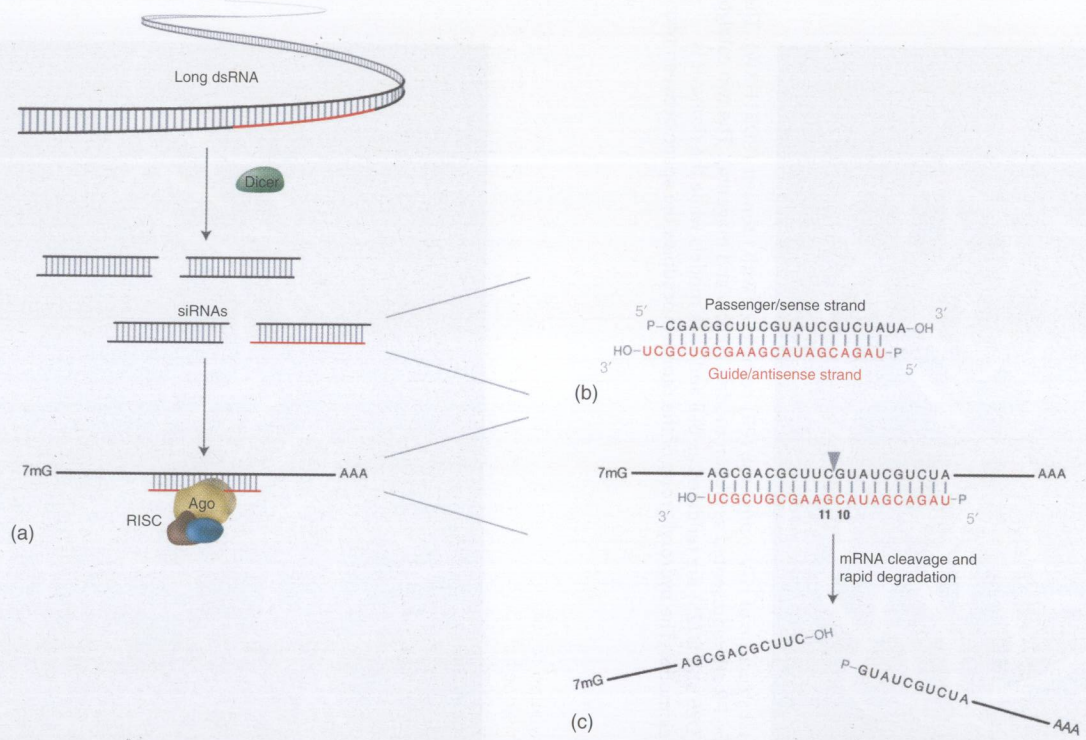

Fig. 1 (p. 603) The RNAi pathway (a) Long dsRNA in the cytoplasm of a cell encounters the enzyme Dicer, which processes the long dsRNA into siRNAs. These siRNAs are unwound and one strand is incorporated into RISC. This guide strand of the siRNA allows RISC to identify target mRNAs and then cleave them, resulting in their degradation. (b) Strand selection of an siRNA. In this example, the strand that will be incorporated into RISC is shown in red, and is designated the guide or antisense strand. This strand is chosen because the first four nucleotides, counting from the 5′ end of the antisense strand of the siRNA, have less thermal stability (A–U rich) than the other strand, which is G–C rich in its first four nucleotides. A helicase activity unwinds this duplex, and hands off one strand to RISC. (c) Target cleavage. The site of the RISC-mediated cleavage is very precise, cleaving between the nucleotides opposite the 10th and 11th bases of the siRNA, counting from the 5′ end of the antisense strand of the siRNA. The RNase H-like cleavage leaves a free hydroxyl on the 5′ region (i.e. the capped end) of the mRNA, and a phosphate on the 3′ half (i.e. the polyadenylated end).

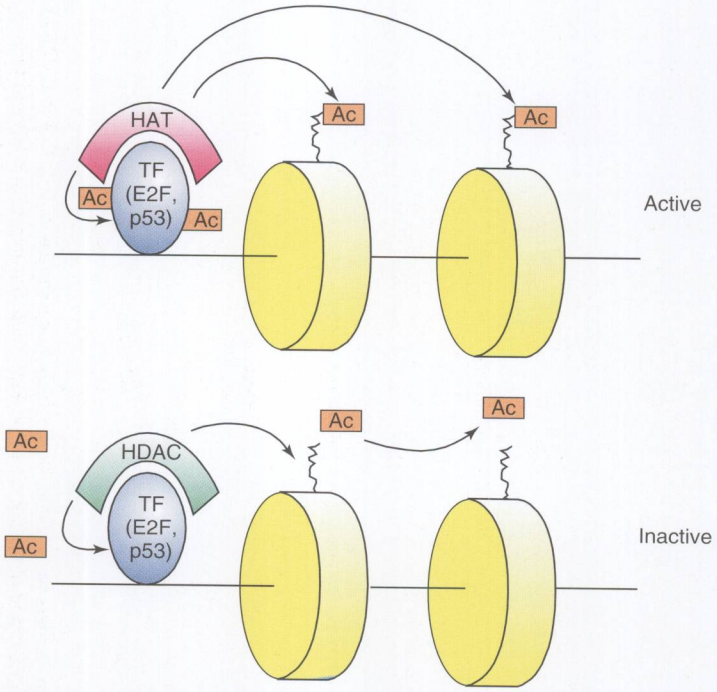

Fig. 4 (p. 764) Acetylation control in the cell cycle. Acetylation (Ac) mediated by acetyltransferases (HATS) can target histone tails in the form of nucleosomes (yellow) or transcription factors (TF) involved in cell cycle control, like E2F and p53. In most cases so far studied, acetylation appears to activate transcription. In contrast, deacetylation mediated by histone deacetylases (HDAC) causes transcriptional inactivity by targeting histones in nucleosomes, leading to a more transcriptionally inert state, together with dampening the activity of transcription factors.

Contents

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