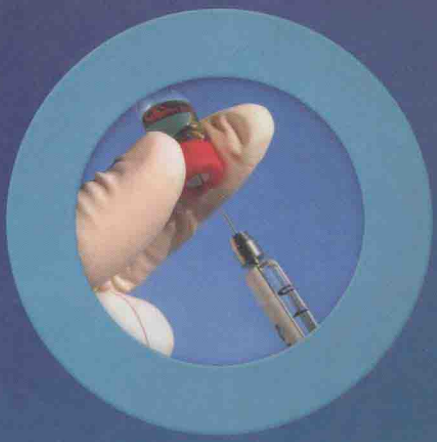

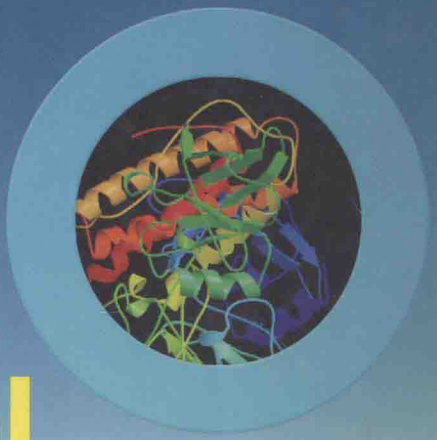

Pharmaceutical Biotechnology

Concepts and Applications

Gary Walsh

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I dedicate this book to my beautiful daughter Alice.
To borrow a phrase:

'without her help, it would have been written in half the time'!

Preface

This book has been written as a sister publication to *Biopharmaceuticals: Biochemistry and Biotechnology*, a second edition of which was published by John Wiley and Sons in 2003. The latter textbook caters mainly for advanced undergraduate/postgraduate students undertaking degree programmes in biochemistry, biotechnology and related disciplines. Such students have invariably pursued courses/modules in basic protein science and molecular biology in the earlier parts of their degree programmes; hence, the basic principles of protein structure and molecular biology were not considered as part of that publication. This current publication is specifically tailored to meet the needs of a broader audience, particularly to include students undertaking programmes in pharmacy/pharmaceutical science, medicine and other branches of biomedical/clinical sciences. Although evolving from *Biopharmaceuticals: Biochemistry and Biotechnology*, its focus is somewhat different, reflecting its broader intended readership. This text, therefore, includes chapters detailing the basic principles of protein structure and molecular biology. It also increases/extends the focus upon topics such as formulation and delivery of biopharmaceuticals, and it contains numerous case studies in which both biotech and clinical aspects of a particular approved product of pharmaceutical biotechnology are overviewed. The book, of course, should also meet the needs of students undertaking programmes in core biochemistry, biotechnology or related scientific areas and be of use as a broad reference source to those already working within the pharmaceutical biotechnology sector.

As always, I owe a debt of gratitude to the various people who assisted in the completion of this textbook. Thanks to Sandy for her help in preparing various figures, usually at ridiculously short notice. To Gerard Wall, for all the laughs and for several useful discussions relating to molecular biology. Thank you to Nancy, my beautiful wife, for accepting my urge to write (rather than to change baby's nappies) with good humour – most of the time anyway! I am also grateful to the staff of John Wiley and Sons for their continued professionalism and patience with me when I keep overrunning submission deadlines. Finally, I have a general word of appreciation to all my colleagues at the University of Limerick for making this such an enjoyable place to work.

Gary Walsh
November 2006

Acronyms

ADCC	antibody-dependent cell cytoxicity
BAC	bacterial artificial chromosome
BHK	baby hamster kidney
cDNA	complementary DNA
CHO	Chinese hamster ovary
CNTF	ciliary neurotrophic factor
CSF	colony-stimulating factor
dsRNA	double-stranded RNA
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
EPO	erythropoietin
FGF	fibroblast growth factor
FSH	follicle-stimulating hormone
GDNF	glial cell-derived neurotrophic factor
GH	growth hormone
hCG	human chorionic gonadotrophin
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
IGF	insulin-like growth factor
ISRE	interferon-stimulated response element
JAK	Janus kinase
LAF	lymphocyte activating factor
LIF	leukaemia inhibitory factor
LPS	lipopolysaccharide
MHC	major histocompatibility complex
MPS	mucopolysaccharidosis
mRNA	messenger RNA
PDGF	platelet-derived growth factor
PEG	polyethylene glycol

PTK	protein tyrosine kinase
PTM	post-translational modification
rDNA	recombinant DNA
RNAi	RNA interference
rRNA	ribosomal RNA
SDS	sodium dodecyl sulfate
ssRNA	single-stranded RNA
STATs	signal transducers and activators of transcription
TNF	tumour necrosis factor
tPA	tissue plasminogen activator
tRNA	transfer RNA
WAP	whey acid protein
WFI	water for injections

Contents

1

Pharmaceuticals, biologics and biopharmaceuticals

1.1 Introduction to pharmaceutical products

Pharmaceutical substances form the backbone of modern medicinal therapy. Most traditional pharmaceuticals are low molecular weight organic chemicals (Table 1.1). Although some (e.g. aspirin) were originally isolated from biological sources, most are now manufactured by direct chemical synthesis. Two types of manufacturing company thus comprise the 'traditional' pharmaceutical sector: the chemical synthesis plants, which manufacture the raw chemical ingredients in bulk quantities, and the finished product pharmaceutical facilities, which purchase these raw bulk ingredients, formulate them into final pharmaceutical products, and supply these products to the end user.

In addition to chemical-based drugs, a range of pharmaceutical substances (e.g. hormones and blood products) are produced by/extracted from biological sources. Such products, some major examples of which are listed in Table 1.2, may thus be described as products of biotechnology. In some instances, categorizing pharmaceuticals as products of biotechnology or chemical synthesis becomes somewhat artificial. For example, certain semi-synthetic antibiotics are produced by chemical modification of natural antibiotics produced by fermentation technology.

1.2 Biopharmaceuticals and pharmaceutical biotechnology

Terms such as 'biologic', 'biopharmaceutical' and 'products of pharmaceutical biotechnology' or 'biotechnology medicines' have now become an accepted part of the pharmaceutical literature. However, these terms are sometimes used interchangeably and can mean different things to different people.

Although it might be assumed that 'biologic' refers to any pharmaceutical product produced by biotechnological endeavour, its definition is more limited. In pharmaceutical circles, 'biologic' generally refers to medicinal products derived from blood, as well as vaccines, toxins and allergen products. 'Biotechnology' has a much broader and long-established meaning. Essentially, it refers

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Table 1.1 Some traditional pharmaceutical substances that are generally produced by direct chemical synthesis

Drug	Molecular formula	Molecular mass	Therapeutic indication
Acetaminophen (paracetamol)	$C_8H_9NO_2$	151.16	Analgesic
Ketamine	$C_{13}H_{16}C/NO$	237.74	Anaesthetic
Levamisole	$C_{11}H_{12}N_2S$	204.31	Anthelmintic
Diazoxide	C_8H_7C/N_2O_2S	230.7	Antihypertensive
Acyclovir	$C_8H_{11}N_5O_3$	225.2	Antiviral agent
Zidovudine	$C_{10}H_{13}N_5O_4$	267.2	Antiviral agent
Dexamethasone	$C_{22}H_{29}FO_5$	392.5	Anti-inflammatory and immunosuppressive agent
Misoprostol	$C_{22}H_{38}O_5$	382.5	Anti-ulcer agent
Cimetidine	$C_{10}H_{16}N_6$	252.3	Anti-ulcer agent

to the use of biological systems (e.g. cells or tissues) or biological molecules (e.g. enzymes or antibodies) for/in the manufacture of commercial products.

The term 'biopharmaceutical' was first used in the 1980s and came to describe a class of therapeutic proteins produced by modern biotechnological techniques, specifically via genetic engineering (Chapter 3) or, in the case of monoclonal antibodies, by hybridoma technology (Chapter 13). Although the majority of biopharmaceuticals or biotechnology products now approved or in development are proteins produced via genetic engineering, these terms now also encompass nucleic-acid-based, i.e. deoxyribonucleic acid (DNA)- or ribonucleic acid (RNA)-based products, and whole-cell-based products.

1.3 History of the pharmaceutical industry

The pharmaceutical industry, as we now know it, is barely 60 years old. From very modest beginnings, it has grown rapidly, reaching an estimated value of US$100 billion by the mid 1980s. Its current value is likely double or more this figure. There are well in excess of 10 000 pharmaceutical companies in existence, although only about 100 of these can claim to be of true international significance. These companies manufacture in excess of 5000 individual pharmaceutical substances used routinely in medicine.

Table 1.2 Some pharmaceuticals that were traditionally obtained by direct extraction from biological source material. Many of the protein-based pharmaceuticals mentioned are now also produced by genetic engineering

Substance	Medical application
Blood products (e.g. coagulation factors)	Treatment of blood disorders such as haemophilia A or B
Vaccines	Vaccination against various diseases
Antibodies	Passive immunization against various diseases
Insulin	Treatment of diabetes mellitus
Enzymes	Thrombolytic agents, digestive aids, debriding agents (i.e. cleansing of wounds)
Antibiotics	Treatment against various infections agents
Plant extracts (e.g. alkaloids)	Various, including pain relief