Klaus Buchholz, John Collins

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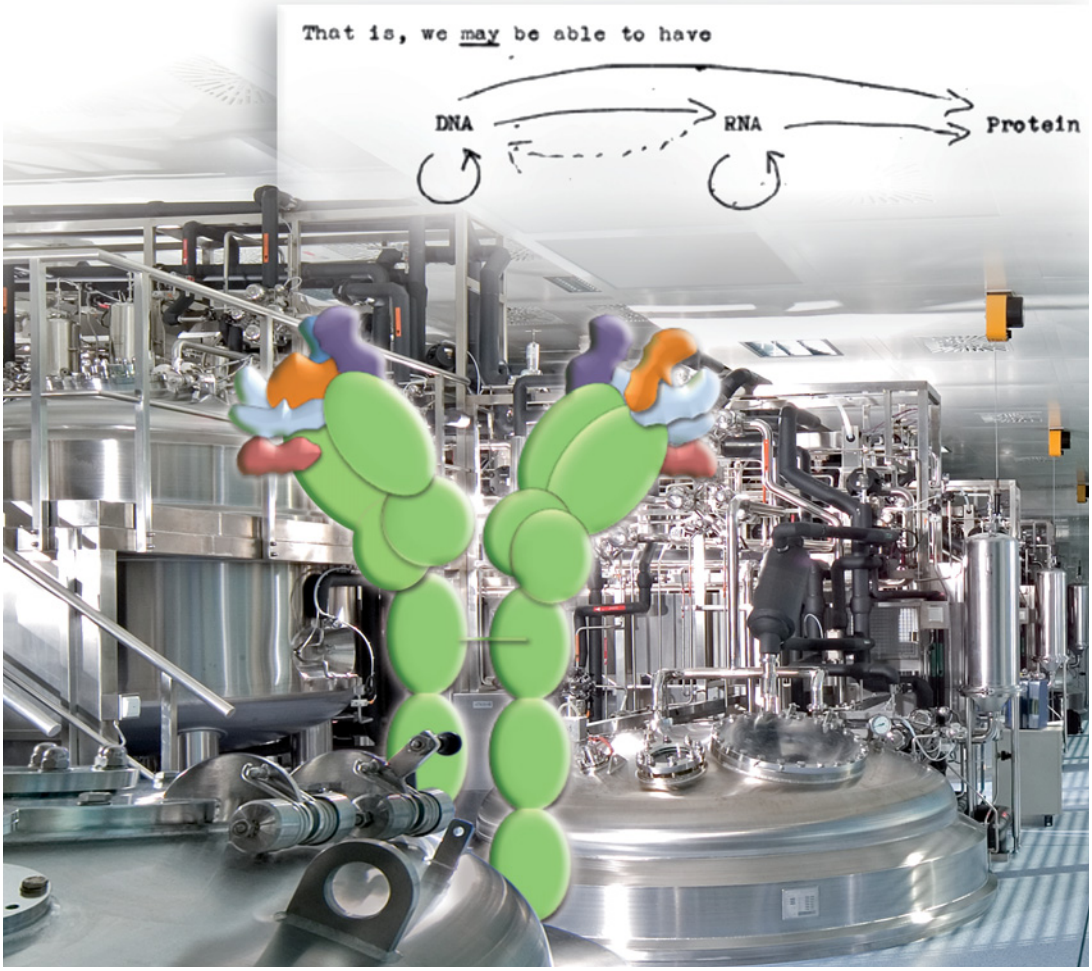
Concepts in Biotechnology

History, Science and Business



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For
Diana and Marie-Christiane

Contents

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Preface

Over the last century the development of *Biotechnology* (BT) has followed fascinating pathways to influence ever more aspects of our lives and to provide significant contributions to the improvement of the quality of life. BT flourished in parallel with biological sciences as a result of insights into the molecular details of genetics and the control of biochemical reactions. Following a long-standing tradition, this knowledge was translated by commercial application for human benefit. It enabled biological pathways to be manipulated and even created for the purpose of manufacturing products and developing processes and services on an industrial scale. Historically, controlled fermentation was used to provide efficient storage for food thus enabling a population to survive periods of cold or drought. By the end of the last century biotechnology had developed into a science and engineering discipline in its own right and is considered to be a field of industrial activity with major economic relevance. The applications of BT extend beyond historical tradition, ranging from production of chemicals, bio-fuels and pharmaceuticals to ensuring a continued supply of clean water.

This book reviews the progress of biotechnology over time and highlights the seminal events in this field. It gives an introduction to the main developments, the principles or concepts, and key researchers involved in pioneering work and in conclusion, attempts to extrapolate to further advances expected in the near future. In view of the extensive range of biotechnological activities it was necessary to concentrate on essentials, illustrated with selected examples, as opposed to using an encyclopedic approach. This book is intended to guide the reader through the diverse fields of activity in BT and encourage further reading in the form of books, specialised reviews and original literature as provided in the reference sections. It is envisaged that the readership of this book will include students of biology, biotechnology and biochemical engineering, in addition to scientists and engineers already engaged in or proposing to work in the fields of BT and related disciplines. It may also serve as a broad introduction to BT for other readers who are interested in an overview of the subject, ranging from historical aspects to the latest developments which are largely a result of the accelerated research in molecular biology and bioinformatics that has taken place over the last 20 years.

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The *historical aspects* of BT are discussed in the opening chapters which highlight the role of inquisitiveness and the thirst for knowledge and understanding of natural processes. This involves a discussion of reputation-building, the interplay of economics and business as well as the role of and dependence on theories. We trace the developments in chemistry and physics that became a prerequisite for the study of the chemical nature of the components involved in biological processes such as brewing, wine and bread making. Heated discussions centring on both the vitalist and chemical theories resulted not only in the emergence of theories and paradigms but also in their reversal. The close interaction of scientists, craftsmen and industry together with significant stimulus, promoted continued research.

Pasteur and Koch established the science of microbiology. A few decades later Buchner finally refuted the last metaphysical hypothesis that processes in living cells required a 'vis vitalis', a vital factor and following this biochemistry emerged as a new speciality. Biotechnological engineering was based on more precise control of the microbial fermentations involved in food processing including large-scale processes for the manufacture of beer, wine, cheese, bread etc. together with the use of sterile starting materials. This led to the subsequent production of fuels and chemical components for polymers and explosives particularly during war time, and the manufacture of antibiotics and vaccines. This in turn stimulated detailed studies on the manufacture of products from microbial fermentations. By the mid-twentieth century, biotechnology had become an accepted speciality.

Basic research in *biochemistry, molecular biology* and *genetics* dramatically broadened the field of life sciences and at the same time unified them by the study of genes and their relatedness throughout the evolutionary process. In Part 2 we discuss the development of this fruitful interplay and describe how it broadened the scope of accessible products and services, at the same time making production cheaper, safer, more reproducible and more reliable. Rapid acceleration of gene and protein analysis caused an explosion of data which led to the emergence of *bioinformatics*. This opened up new avenues for medical analysis that was orientated more towards preventive measures rather than corrective intervention. This is a continuing trend which is substantiated by the prediction that during the next few years affordable analysis of the complete genetic potential of an individual will be available within hours. New areas of research have evolved such as *systems biology* in which living systems can be successfully modelled as networks of ever-increasing complexity. As the volume of information increases and modelling improves so does the probability that insight into potential targets for pharmaceuticals can be better translated into developing successful medicines. To foster such aims, centres for translational medicine are being founded in many cities where medical schools and hospitals participate in close interactions with basic research institutes.

The understanding of the fundamental *programming of animal cells* in the developing embryo and in particular the discovery of a small number of proteins capable of guiding stem cell differentiation and even the reprogramming of already differentiated cells, has opened up perspectives for a completely new and very exciting branch of biotechnology in the area of tissue and organ synthesis for *regenerative medicine*. In combination with advances in fertility medicine this has also led to the

cloning of animals and the production of *transgenic animals*. One aspect of this technology is the use of tissue cloning to produce human tissue cultures as models for inherited disease.

In Part 3 we discuss engineering and applied topics. *Biochemical and bioprocess engineering* constitute the basis for translating scientific innovation and development into industrial processes. They represent an interdisciplinary field based on molecular biology, biochemistry and engineering disciplines. As a result of the progress in molecular biology, new tools known as the 'omics' were developed: genomics, proteomics and metabolomics, to mention only the most common. *Biosystems engineering* or systems biotechnology, integrates the approaches and the extensive volume of data derived from these specialities and from bioreaction engineering in a 'holistic' approach, using bioinformatics tools.

Industrial biotechnology, with its historical roots, continues in diverse industrial fields of activity including food and feed and commodities such as enzymes for use in detergents, bio-fuel and energy production, polymer manufacture and the development and production of many drug constituents, as well as providing services, for example in waste treatment and other processes related to environmental protection.

The approval in 1982 of recombinant human insulin produced in *E. coli* and developed by Genentech in cooperation with Eli Lilly in the late 1970s, was an historical landmark. By 2006, some 165 biopharmaceuticals had been approved in the EU and/or the USA for human use. This illustrates the emergence and rise of recombinant technologies which constitute the basis of *pharmaceutical biotechnology*. Today, approximately one in four of all genuinely new drugs currently entering the market is a biopharmaceutical and in 2008 over 400 biopharmaceuticals were in various stages of clinical evaluation. These include hormones, soluble hormone receptors (as hormone antagonists), blood factors, thrombolytics, interferons, monoclonal antibodies, vaccines and therapeutic enzymes. Selected aspects of engineering and production processes together with information relating to their use are discussed in this chapter. Data on industrial development, products, companies and economics are also presented.

The potential of transgenic *plant biotechnology* is to create crops that produce higher yields and are able to grow on less fertile land in order to feed the growing world population. Crops should be resistant to pests and require less chemical treatment, notably with insecticides, fungicides, herbicides and fertilizers, and exhibit low environmental impact. The majority of agricultural scientists are convinced that such crops can be delivered by the exploitation of molecular breeding strategies. Food production has risen considerably over the decades in terms of a 'Green Revolution', most notably in developing countries, but the increase in per capita food supply has been small. Hence research in recombinant food production is considered to be a necessary part of the strategies to ensure adequate nutrition. Nevertheless, debates over the risks of the technology have evoked conflicts and created a critical, even negative publicity, particularly in Western Europe.

BT offers in general a sustainable method of production, based mostly on renewable resources with minimal or no waste and by-products that can be recycled or reused, for example as feed components. There are manifold interactions with

political, social, economic and environmental issues. Laws, regulations and ethical concerns pertinent to biotechnology are important topics of discussion although there are dramatic differences in legislation between countries. Current efforts are centred around establishing common global regulations including the removal of unfair unilateral advantages and support for health care and economies in developing countries. The regulatory influences which affect how science is carried out and technology is applied are addressed in each chapter. In addition to the underlying scientific concepts, further information is presented in each chapter on the use of products, along with data on industrial activities and production.

The increase in computing power due to the invention and continued development of microchips via nanotechnology has pioneered and driven a revolution in communication during the last three decades. At least one computer, television and mobile telephone have found their place in essentially every home. Biotechnology has also undergone a corresponding development, although perhaps not so immediately identifiable at the level of consumer goods in the shops. There is, however, hardly an area of human activity which has not been affected by the recent biotechnological revolution. We hope that after completing our book, the readers will feel that they have a better understanding of how and why this revolution took place, its roots and its further potential to improve so many aspects of our lives.

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Abbreviations and Glossary

Acre	4046 m^2
ADM	Archer Daniels Midland (starch producing and converting company, USA)
ADP	adenosine diphosphate
7-ACA	7-Aminocephalosporanic acid
7-ADCA	7-Aminodesoxycephalosporanic acid
6-APA	6-Aminopenicillanic acid
AIChE	American Institute of Chemical Engineers
AMP	adenosine monophosphate
Array CGH	Array *Comparative Genome Hybridization*, for example for comparing (malignant) biopsy material with DNA from normal tissue
ATP	adenosine triphosphate
BAC libraries (BACs)	bacterial artificial chromosome libraries
BHK	baby hamster kidney (cells)
BMP	bone morphogenetic protein
BMS	Bristol Meyers Squibb (USA)
bn	billion
BOD	Biological oxygen demand (of waster water)
BP	Before present
BPTI	Bovine pancreatic trypsin inhibitor
BT	Biotechnology
Bt	*Bacillus thuringiensis*
C&EN	Chem. Eng. News
CCD	computational cell dynamics
cDNA	copy DNA, reverse transcribed from mRNA
CDR	complementarity-determining region of an antibody
CEPH	Centre d'études des polymorphisms humains, Paris, France (The Centre for the Study of Human Polymorphisms)
CFD	computational fluid dynamics
CFTR	Cystic fibrosis transmembrane conductance regulator
cGMP	current Good Manufacturing Practice

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CHO	Chinese hamster ovary (cells)
CIP	clean in place
CMV	Cytomegalie virus
CNV	copy number variation
CP	capsid or coat protein (of virus)
CSF	Colony stimulating factor
Cultivars	cultivated plant varieties
2D	two dimensional
DARPins	Designed Ankyrin Repeat Proteins
2DE	two dimensional electrophoresis
2DE IEF/SDS-PAGE	two dimensional electrophoresis combined with IEF and SDS-PAGE
DGT	direct gene transfer (including particle bombardmet)
DHA	docosahexanoic acid
dm	dry matter
2D-PAGE	two-dimensional gel electrophoresis
2DE IEF/SDS-PAGE	two dimensional electrophoresis method
DH	dehydrogenase
DOE US	Department of Energy, United States of America
DPN^+	diphosphonucleotide (is identical with NAD^+)
DPNH	hydrogenated diphosphonucleotide (is identical with NADH)
dt/ha	decitonnes (0,1 t) per hectare
€	EURO, 1.40 $ (Oct. 2010, mean)
EBIT	earnings before interest and taxes
E. coli	*Escherichia coli*
EF	environmental factor
EI	environmental index
ELISA	enzyme linked immunosorbent assay
EMEA	European authority for approval of pharmaceuticals
EP	epothilone
EPA	Environmental Protection Agency (USA)
EPA	eicosapentanoic acid
Epitope	specific region on a protein recognized by an antibody
EPC	European patent convention (5 October 1973)
EPO	European patent office or Erythropoietin
ER	endoplasmatic reticulum
ESC or ES	embryonic stem cells
ESI-MS	electrospray-ionisation mass spectrometry
ESI-TOF MS/MS	electrospray-time of flight-mass spectrometry
EST	expressed sequence tags; short DNA fragments obtained by random sequencing of clones from cDNA libraries
EU	European Union
FAO	Food and Agriculture Organization (USA)
FBA	flux balance analysis

FDA	Food and Drug Administration (USA)
FDP	fructose-1,6-diphosphate
Fluxome	flux distribution of the central metabolic pathways
Ft.	feet (30.5 cm)
Gal	gallon (3,78 L)
GC-MS	coupled gas chromatography-mass spectrometry
GM	genetically modified;
GMO	genetically modified organism
GRAS	generally recognized as safe
GMP	Good Manufacturing Practice
GPCRs	G protein coupled receptors
GSK	GlaxoSmithKline
ha	hectar, 10 000 m2
hGH	human growth hormone
HIV	Human immunodeficiency virus
hl	hectoliter (100 l)
HR	hypersensitive response
HTS	high throughput screening
IEF	isoelectric focusing
IFN	interferon
IgG	immune globulin G
IL	interleukin
In.	inch (2.54 cm)
i.v.	intravenous
JACS	Journal Am. Chem. Soc.
J&J	Johnson & Johnson
LC-MS	liquid chromatography-mass spectrometry
LD (LOD score)	linkage disequilibrium in population genetics
LRR	leucine-rich-repeat proteins, for example ankyrin
mAB	monoclonal antibody
MALDI-TOF-MS	Matrix-Assisted-Laser-Desorption/Ionization – Time-Of-Flight-Mass-Spectrometry
MDR	multi drug resistant
MFA	metabolic flux analysis
MI	mass Index
miRNAs	micro RNAs
mn	million
Mtoe	million tons oil equivalents
Mw	molecular weight, molar mass
m-Arrays	micro-arrays
NAD	Nicotinamide-adenine-dinucleotide
NADH	hydrogenated NAD
NBF	new BT firm
NCE	new chemical entity
NGOs	non governmental organizations

NIH	National Institutes of Health (USA)
NK cells	natural killer cells
NMR	nuclear magnetic resonance
NRRL	Northern Regional Research Laboratory (USA)
NSO	mouse myeloma derived mammalian cells
ON	oligonucleotides
ORF	open reading frame
OS	oligosaccharides
OTA	Office of Technology Assessment (USA)
PAGE	polyacrylamide gel electrophoresis
PAT	process analytical technology
PDO	1,3-propanediol
PDR	pathogen-derived resistance
PEG	polyethylene glycol
PEGylation	attachment of polyethylene glycol
PET	positron emission tomography
PHB	polyhydroxybutyrate (a polyester)
pI	Ionic strength (logarithmic scale)
Plastids	Intracellular organelles, e.g., chloroplasts that have their own double stranded DNA
pO_2	oxygen partial pressure
Pound	453 g
PR	pathogenesis related
PR	plant disease resistance
PS	iPS and piPS Pluripotent stem cells, induced pluripotent stem cells, protein-induced pluripotent stem cells
PSTI	Human pancreatic secretory trypsin inhibitor
QTL	quantitative trait locus
QM	quality management
R	resistance (genes)
rasiRNAs	repeat-associated small interfering RNA.s
R&D	research and development
rDNA	recombinant DNA
rDNA technologies	recombinant DNA technologies
rh	recombinant human
RNAi	interfering RNA, RNA interference
rPC	real time PCR
rRNA	ribosomal RNA
$	US $, corresponding to 0,71 € (Oct. 2010, mean)
SAGE	serial analysis of gene expression
SDA	stearidonic acid
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC	size exclusion chromatography
SIP	sterilization in place
siRNA	small interfering RNA

shRNA	short hairpin RNA
SNP	single nucleotide polymorphism
STR	stirred tank reactor
SUB	single use bioreactor
t/a	tonnes per year
™	trade mark
TNF	Tumor necrosis factor
tPA	Tissue plaminogen activator
Translation capacity	the number of times a transcript is translated.
USDA	US Department of Agriculture
US$	US dollar (see $)
YAC libraries.	yeast artificial chromosome. libraries

Part One
History

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