Pharmacological Reports
2013, 65, 1102–1111
ISSN 1734-1140

Review

Biotechnology and genetic engineering in the new drug development. Part III. Biocatalysis, metabolic engineering and molecular modelling

Agnieszka Stryjewska[1], Katarzyna Kiepura[1], Tadeusz Librowski[2], Stanisław Lochyński[3]

[1]Department of Bioorganic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wyb. Wyspiańskiego 27, PL 50-370 Wrocław, Poland

[2]Department of Radioligands, Medical College, Faculty of Pharmacy, Jagiellonian University, Medyczna 9, PL 30-688 Kraków, Poland

[3]Institute of Cosmetology, Wrocław College of Physiotherapy, Kościuszki 4, PL 50-038 Wrocław, Poland

Correspondence: Stanisław Lochyński, e-mail: s.lochynski@wsf.wroc.pl; Tadeusz Librowski, e-mail: mflibrow@cyf-kr.edu.pl

Abstract:
Industrial biotechnology has been defined as the use and application of biotechnology for the sustainable processing and production of chemicals, materials and fuels. It makes use of biocatalysts such as microbial communities, whole-cell microorganisms or purified enzymes. In the review these processes are described.
Drug design is an iterative process which begins when a chemist identifies a compound that displays an interesting biological profile and ends when both the activity profile and the chemical synthesis of the new chemical entity are optimized. Traditional approaches to drug discovery rely on a stepwise synthesis and screening program for large numbers of compounds to optimize activity profiles. Over the past ten to twenty years, scientists have used computer models of new chemical entities to help define activity profiles, geometries and relativities. This article introduces *inter alia* the concepts of molecular modelling and contains references for further reading.

Key words:
biotechnology, metabolic engineering, gene therapy, viral vectors, non-viral vectors, artemisinin, lovastatin

Introduction

Given the different approaches existing on the definition of 'biotechnology', and the plurisemic use of the term, it seems necessary to briefly introduce its potential different meanings. Biotechnology makes reference to the activity consisting of the utilization or manipulation of living organisms for obtaining products or implementing processes, generally by means of the integration of natural and engineering sciences [25].

Similarly, diverging approaches exist also in respect of the meaning of certain bioproducts, such as biopharmaceuticals. Although biopharmaceutical is

a widely used term, it is not always employed with the same meaning. There are several possible notions of what a biopharmaceutical is.

The first definition, which is the most widely accepted, alludes to biopharmaceuticals as medicinal products, therapeutics, prophylactics and *in vivo* diagnostics with active ingredients inherently biological in nature and manufactured using biotech.

A second definition limits biopharmaceutical products to those fulfilling the first definition and involving genetic engineering. This corresponds to what has been named "new or modern biotech", which is a subset of the abovementioned notion. Since the early eighties, when recombinant DNA and hybridoma technology were developed, the recourse to this notion has become more and more usual. This was, for instance, the definition used by the Federal Trade Commission in its 2009 report on biosimilars. According to the Federal Trade Commission, "biologic drugs are protein-based and derived from living matter or manufactured in living cells using recombinant DNA biotechnologies". As it can be observed, this approach limits the concept of 'biologic drugs'.

Another definition of 'biopharmaceutical' implies a contagious use of the term. This can be observed when any health-care product that is loosely related to biotechnology is deemed to be a 'biopharmaceutical'. For instance, all products manufactured by a company that produces biopharmaceuticals would be considered biopharmaceutical products.

Finally, another possible approach, widely used among those working in the commercial and media areas of the pharmaceutical industry, employs the term 'biopharmaceutical' as a synonym of anything that is pharma-related.

Therefore, although references are made to other biopharmaceuticals that fall under the first definition, most problems arise in relation to modern biotechnological products which, hence, frequently are the focus of attention [9].

In the years 1971–1973, new technology was brought into effect, which became a great scientific turning point. It was recombinant DNA technology, also known as genetic engineering, which until today has formed the base of many biotechnological processes. Polymerase Chain Reaction is one of elements of the technology of recombined DNA. The technique discovered in 1985 by Mullis enables researchers to produce millions of copies of a specific DNA sequence in approximately two hours. This automated process bypasses the need to use bacteria for amplifying DNA [4].

The basic biotechnological processes used most widely in the pharmaceutical industry apart from recombined DNA technology, also including directed mutagenesis, are biocatalysis, technology of monoclonal antibodies, technology of vaccines, metabolic engineering, and, only recently, gene therapy [9, 13, 25] as well. However, these processes are largely based on the tools of gene engineering. Biotechnology has a major impact on the pharmaceutical industry.

Biocatalysis

Biocatalysis is a process used for the transformation or manufacturing of certain products using a biocatalyst, which may be an enzyme, an enzyme complex, organelle, or an entire cell, that is either growing or not. Biocatalysts are used as free and immobilized forms. They may be of microbial origin, or from an animal or plant. The substrate combines with them in bioreactors, where suitable reaction conditions are set up [1]. Biocatalysts also accelerate the reaction that occurs repeatedly. The main advantage of biocatalysis is the possibility to obtain chiral products, essential in the pharmaceutical industry [21].

Biocatalysis carried out in the forms listed below:

1. Fermentation – the use of living cells in bioreactors for the transformation of simple substrates, such as sugar or methanol, into the desired product.
2. Fermentation of precursors – similar to the above, using living cells for the transformation of more complex substrates, or intermediates.
3. Biotransformation – the transformation of the precursor into the product by enzymes or an undivided cell, in several stages.
4. Enzyme catalysis – crude extracts or partially purified enzymes are used for the transformation.
5. Purified enzymes – used mainly in the pharmaceutical industry [6].

The process of biocatalysis depends on the stability of the protein and enzyme kinetics as well as other properties associated with the ongoing reaction. To perform efficient biocatalysis, a suitable biocatalyst must first be obtained. It is also necessary to establish the process and determine whether it will be efficient