Biotechnology: Introduction, Scope and Applications of Biotechnology

Introduction:

Biotechnology is defined as the 'application of scientific and engineering principles to the processing of material by biological agents to provide goods and services'. The Spinks Report (1980) defined biotechnology as 'the application of biological organisms, systems or processes to the manufacturing and service industries'. United States Congress's Office of Technology Assessment defined biotechnology as 'any technique that used living organisms to make or modify a product, to improve plants or animals or to develop microorganisms for specific uses'. The document focuses on the development and application of modern biotechnology based on new enabling techniques of recombinant-DNA technology, often referred to as genetic engineering. The history of biotechnology begins with zymotechnology, which commenced with a focus on brewing techniques for beer. By World War I, however, zymotechnology would expand to tackle larger industrial issues, and the potential of industrial fermentation gave rise to biotechnology. The oldest biotechnological processes are found in microbial fermentations, as born out by a Babylonian tablet circa 6000 B.C. unearthed in 1881 and explaining the preparation of beer.

In about 4000 B.C. leavened bread was produced with the aid of yeast. The Sumerians were able to brew as many as twenty types of beer in the third millennium B.C. In the 14th century, first vinegar manufacturing industry was established in France near Orleans.

In 1680 Antony Van Leeuwenhoek first observed yeast cells with his newly designed microscope. In 1857, Louis Pasteur highlighted the lactic acid fermentation by microbe.

By the end of 19th century large number of industries and group of scientists were involved in the field of biotechnology and developed large scale sewage purification system employing microbes were established is Germany and France.

In 1914 to 1916, Delbruck, Heyduck and Hennerberg discovered the large-scale use of yeast in food industry. In the same period, acetone, butanol and glycerin were obtained from bacteria.

In 1920, Alexander Fleming discovered penicillin and large scale manufacturing of penicillin started in 1944.

Table 22.1. Historical development of biotechnology.

Year	Development
Before 6000 B.C.	Yeast employed to make wine and beer
4000 B.C.	Leavened bread produced with the aid of yeast
1521	Aztecs harvested algae from lakes as a source of food.
1670-1680	Copper mined with aid of microbes, Rio Tinto, Spain.
	Antoine van Leeuwenhoek first observed microbes with newly designed microscope.
1869	Johann Meischer isolated DNA from the nuclei of white blood cells.
1876	Louis Pasteur identifies extraneous microbes as a cause of failed beer fermentations
1890	Alcohol first used to fuel motors
1893	Fermentation process patented by Koch, Pasteur.
1897	Edurad Buchner discovered that enzymes extracted from yeast can convert sugar into alcohol.
1910	Thomas H. Morgan proved that genes are carried on chromosomes "Biotechnology" term coined.
	Large-scale sewage purification systems employing microbes are established.
1912-1914	Three important industrial chemicals- acetone, butanol and glycerol were obtained from bacteria.
1918	Germans use acetone produced by plants to make bombs.
	Yeast grown in large quantities for animal and glycerol.
1920	Alexander Fleming discovered penicillin.
	Plant hybridization.
1928	Yeast grown in large quantities for animal and glycerol.
1938	Proteins and DNA studied by X-ray crystallography.
1941	George Beadle proposed "one gene, one enzyme" hypothesis.
1943-1953	Linus Pauling described sickle cell anemia calling it a molecular disease. Cortisone made in large amounts.
	DNA identified as the genetic material.

1944	DNA as genetic material and transformation factor in bacteria (Avery, Macleod and McCarty).
1946	Bacterial recombination discovered (Lederberg and Tatum)
1951	Lambda bacteriophage discovered (Lederberg)
1953	Double helix structure of DNA revealed (Watson and Crick).
1956	Isolation of DNA polymerase I, enzymatic synthesis of DNA (Kornberg).
1958	Semiconservative replication of DNA (Messelson and Stahl).
1960	Isolation of mRNA.
1961	Nucleic acid hybridization (Marmur and Doty), Operon model (Jacob and Monod) and *in vitro* protein synthesis allows codon assignment (Nirenberg and Mathaei).
1962	Mining of uranium with the aid of microbes begin in Canada.
1973	Beginning of genetic engineering. Stanley Cohen produced first recombinant DNA organism.
	Brazilian government initiates major fuel programme to replace oil with alcohol.
1975	Hybridomas which make monoclonal antibodies were first created
1976	US National Institute of Health introduces guidelines on genetic engineering
1977	Human Growth Hormone produced by bacterial cells.
1978	Genetic engineering techniques used to produce human insulin in *E. coli* by Genentech Inc.
1979	Genentech Inc. produce human growth hormone and two kinds of interferon DNA from malignant cells transformed a strain of cultured mouse cells - new tool for analyzing cancer genes.
1980	Rank Hovis McDougall receives permission to market fungal food for human consumption in UK.
	The US Supreme Court rules in Diamond v. Chakrabarty that genetically engineered microorganisms can be patented.
1981	Monoclonal antibodies receive US approval for use in diagnosis.
1982	The Food and Drug Administration approves the first biotechnology therapy, a human insulin drug made by Genentech.
1983	Syntex Corporation received FDA approval for a monoclonal antibody-based diagnostic test for *Chlamydia trachomatis*.
1984	Chiron Corp. announced the first cloning and sequencing of the entire human immunodeficiency virus (HIV) genome.
	Stanford University received a product patent for prokaryote DNA.
	Charles Cantor and David Schwartz developed pulsed-field gel electrophoresis.
	Animal interferon's approved for protection against cattle disease.
1985	Genetically engineered plants resistant to insects, viruses, and bacteria were field tested for the first time.
	Axel Ullrich reported the sequencing of the human insulin receptor
	Plants can be patented.
1986	Orthoclone OKT3® (Muromonab-CD3) approved for reversal of acute kidney transplant rejection.
	The EPA approved the release of the first genetically engineered crop, gene-altered tobacco plants
1987	Genentech received FDA approval to market rt-PA (genetically engineered tissue plasminogen activator) to treat heart attacks.
	Recombivax-HB® (recombinant hepatitis B vaccine) approved.

1989	Epogen® (Epoetin alfa) a genetically engineered protein introduced, providing a means to help patients with kidney failure.
1990	GenPharm International, Inc. created the first transgenic dairy cow. The cow was used to produce human milk proteins for infant formula.
	The Human Genome Project, the international effort to map all of the genes in the human body, was launched.
	The first successful field trial of genetically engineered cotton plants was conducted by Calgene Inc. The plants had been engineered to withstand use of the herbicide Bromoxynil.
1993	Kary Mullis won the Nobel Prize in Chemistry for inventing the technology of polymerase chain reaction
1994	The first genetically engineered food product, the Flavr Savr tomato, gained FDA approval.
1996	Dolly the sheep is cloned.
1997	Researchers at Scotland's Roslin Institute report that they have cloned a sheep--named Dolly--from the cell of an adult ewe. Polly the first sheep cloned by nuclear transfer technology bearing a human gene appears later.
	A group of Oregon researchers claim to have cloned two Rhesus monkeys.
	Rituxan, the first antibody-based therapy for cancer (for patients with non-Hodgkin's lymphoma) was approved.
	A new DNA technique combines PCR, DNA chips, and computer programming providing a new tool in the search for disease-causing genes.
1998	Human embryonic stem cell lines are established.
	University of Hawaii scientists, clone three generations of mice from nuclei of adult ovarian cumulus cells.
2000	"Working draft" of the human genome's 3.15 billion letters is completed after a decade of research.
2003	Broad Institute is founded in Cambridge to give scientists access to the human genome project, and to understand the molecular basis of disease.
2007	Craig C. Mello, a University of Massachusetts researcher, shares the Nobel Prize with Andrew Fire of Stanford University for discovering a special kind of RNA that can shut down individual genes.

Scope of Biotechnology:

Genetic engineering in biotechnology stimulated hopes for both therapeutic proteins, drugs and biological organisms themselves, such as seeds, pesticides, engineered yeasts, and modified human cells for treating genetic diseases. The field of genetic engineering remains a heated topic of discussion in today's society with the advent of gene therapy, stem cell research, cloning, and genetically-modified food.

Biotechnology is the applied science and has made advances in two major areas, viz., molecular biology and production of industrially important bio-chemical. The scientists are now diverting themselves toward biotechnological companies; this has caused the development of many biotechnological industries.

In USA alone more than 225 companies have been established and successfully working, like Biogen, Cetus, Geneatech, Hybritech, etc. In world, USA, Japan, and many countries of Europe are leaders in biotechnological researchers encouraged by industrialists.

These companies are working for human welfare and opted following areas for research and development:

(a) Automated bio-screening for therapeutic agents.
(b) Bio-processing alkenes to valuable oxides and glycols.
(c) Developing immobilized cell and enzyme systems for chemical process industries.
(d) Engineering of a series of organisms for specific industrial use.
(e) Genetical improvement of microorganisms for production of pharmaceutical products.
(f) Human gene therapy.
(g) Improved production of Vitamin B12.
(h) Large-scale production of fructose from inexpensive forms of glucose.
(i) Manufacturing ethanol by continuous fermentation.
(j) Microbiological based production of human insulin and interferon's.
(k) Microbiologically up-gradation of hydrocarbons.
(l) Production and development of vaccine to prevent calibacillosis.
(m) Production of bio-pesticide and bio-fertilizers.
(n) Production of diagnostic kits for toxoplasmosis identification.
(o) Production of monoclonal antibodies for organ transplant tissue typing.
(p) Production of photo-synthetically efficient plants.
(q) Production of transgenic plants and animals.
(r) Production of xanthan gum in oil fields for recovery of crude mineral oils.

The advances in recombinant DNA technology have occurred in parallel with the development of genetic processes and biological variations. The development of new technologies have resulted into production of large amount of biochemically-defined proteins of medical significance and created an enormous potential for pharmaceutical industries.

Biotechnology in itself is a vast subject and its scope is extended to various branches of biology. This includes plant tissue culture, production of transgenic in

animal and plants, applications in medicine as tools and therapeutics, creation of new enzymes and their immobilization for industrial use, development of monoclonal antibodies and control of pollutions, etc.

Applications:

Industrial Applications of Biotechnology:

The industrial application of molecular biotechnology is often subdivided, so that we speak of red, green, gray or white biotechnology. This distinction relates to the use of the technology in the medical field (in human and animal medicine), agriculture, the environment and industry.

Some companies also apply knowledge deriving from molecular biotechnology in areas that cut across these distinctions (e.g., in red and green biotechnology, sequencing services). According to an investigation by Ernst and Young relating to the German biotech industry, 92% of companies are currently (2004) working in the field of red biotechnology, 13% in green, and 13% in gray or white biotechnology.

Biotechnology in Medicine:

Biotechnology products for therapeutic use include a very diverse range of products.

Some products are intended to mimic the human counterpart, whereas others are intended to differ from the human counterpart and may be analogues, chemically modified (e.g., pegylated) or novel products (e.g., single chain or fragment antibody products, gene transfer vectors, tissue-engineered products).

Most of these products are regulated as medicinal products; however, the regulatory status of others such as some cell therapies and tissue: organ-based products differs globally and falls within the borderline between the practice of medicine, medical devices and medicinal products. Different areas of medicine in which biotechnology is used to develop diagnostic kits and cure are depicted in figure.

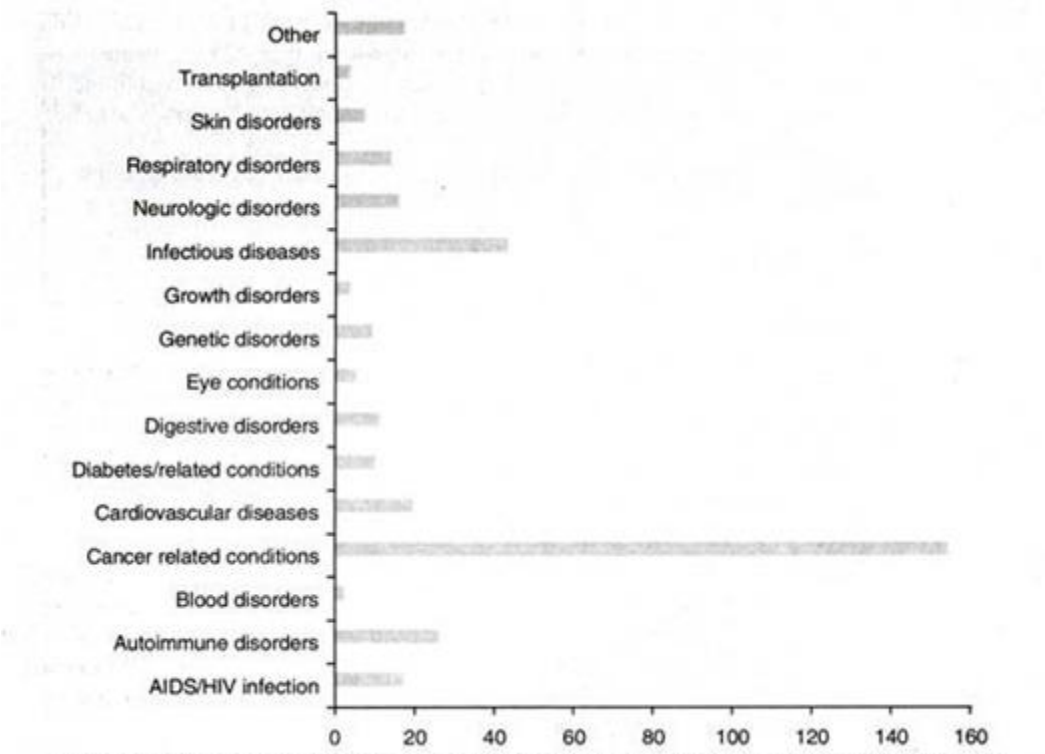

Fig. 22.1. Different areas of medicine in which efforts are being made with the help of biotechnology.

Biotechnology-derived pharmaceuticals may be derived from a variety of expression systems such as Escherichia coli, yeast, mammalian, insect or plant cells, transgenic animals or other organisms. The expressed protein or gene may have the identical amino acid or nucleotide sequence as the human endogenous form, or may be intentionally different in sequence to confer some technical advantage such as an optimized pharmacokinetic or pharmacodynamics profile.

The glycosylation pattern of protein products is likely to differ from the endogenous human form due to the different glycosylation preferences of the expression system used. Furthermore, intentional post-translation modifications or alterations may be made such as pegylation. It is important for the toxicologist to be aware of the nature of the product to be tested in terms of primary, secondary and tertiary structure, and any post-translational modifications such as glycosylation status, particularly as these may be altered if the manufacturing system is modified.

Table 22.4. Biotechnological products in medicine.

Class	Products
Hormones	Follicle stimulating hormone, growth hormone, insulin, insulin analogues
Growth factors	Platelet-derived growth factor, nerve growth factor, insulin growth factor-1
Cytokines	Interferones, interleukins, colony stimulating factor, erythropoietin
Vaccines	Conventional, recombinant protein antigen, modified bacteria or viruses
Nucleic acid based products	Gene therapy, DNA vaccines, ribozymes
Cell, tissue & organs	Autologous, xenoxenix
Others	Clotting factors, enzymes

Red Biotechnology:

Within the field of red biotechnology, which deals with applications in human and animal medicine, there are various further distinctions that can be made: biopharmaceutical drug development, drug delivery cell and gene therapies, tissue engineering/regenerative medicine, pharmacogenomics (personalized medicine), system biology, and diagnosis using molecular medicine.

Biopharmaceutical Drug Development:

In the field of biopharmaceutical drug development, it is the development of therapeutic human proteins by recombinant methods. (Table 22.5) for use as medicines that has the longest tradition. As mentioned above, recombinant human insulin was the first recombinant medicine in the world, produced by Genentech and brought to market in 1982. Today, recombinant human insulin has almost completely driven the other preparation of insulin (isolated from human or animal tissues) from the market.

Table 22.5. Selected examples of recombinant proteins with indication and manufacturer.

Drug	Product name	Indication	Manufacturer
Human insulin	Humulin	Diabetes mellitus type I	Eli Lilly
Somatotropin	Humatrope	Inadequate growth	Eli Lilly
Erythropoietin alpha	Erypo/Epogen	Anemia	Jansen-Cilag/Amgen
Factor VIII	Bioclate/Kogenate	Hemophilia	Centeon/Bayer
Interferon alpha 2 a	Roferon A	Cancer	Roche
Interferon beta 1 b	Betaferon	Mulitples sclerosis	Schering
Tissue plasminogen activator tPA (alteplase)	Actilyse	Thrombolytic agent	Boehringer Ingelheim

The first therapeutic antibodies, especially monoclonal antibodies, have been on the market since the late 1990s. In 2002, antibodies were (along with vaccines) the most important therapeutic class of drugs under development and there are also

more recent market studies more than 100 antibodies or antibody fragments were at the clinical development stage in 2002 and research and development is being carried out on around 470 more in about 200 companies around the world .

Since the introduction of therapeutic antibodies onto the market, they have achieved significant turnovers, which are growing continually. The market for 2008 is estimated at a volume of US $16.7 billion (from Data-monitor, November 2003). Today, in addition to proteins, which currently play the most significant role in the biopharmaceutical field, new types of drugs based on RNA (antisense drugs, ribozymes, aptamers, Spiegelmers and RNA interference) are also being developed on the basis of advances in knowledge on molecular biotechnology.

Table 22.6. Selected examples of approved monoclonal antibodies.

Drug	Product name	Indication	Manufacturer
Abciximab	Reopro	Anticoagulant	Eli Lilly
Centocor Europe			
Trastuzumab (anti-HERA2-a)	Herceptin	Breast cancer	Roche
Adalimumab (anti-TNF-alpha)	Humira	Rheumatoid arthritis	Abbott
Infliximab (anti-TNF-alpha)	Remicade	Crohn's disease	Centocor
Alematuzumab (anti CD52)	Campth	Leukemia	Millennium &Ilex

Table 22.7. Selected examples of therapeutic RNAs on the market or under development.

Principle of action	Product name/production stage	Indication	Company
Antisense	Vitravene/market	CMV retinitis	ISIS pharmaceuticals
Antisense	Affinitak/phase II	Cancer	ISIS pharmaceuticals
Antisense	Alicaforsen/phase III	Crohn's disease	ISIS pharmaceuticals
Antisense	AP 12009/phase II	Brain tumor	Antisense pharma
Ribozyme	ANGIOZYME/phase II	Intestinal cancer	Sirna therapeutics

Drug Delivery:

Closed linked to the development of therapeutic agents are the means of achieving their targeted delivery to their site of action. These drug delivery systems are mainly used for drugs whose physical and chemical characteristics make them insufficiently stable in reaching their site of action intact. They can also be used to transport drugs in a targeted way to particular sites of action (tissue specific targeting), or to overcome biological barriers such as the intestinal wall or the blood-brain barrier.

Green Biotechnology:

Green biotechnology is the application of biotechnology processes in agriculture and food production. The main dominant forces in green biotechnology today are agro giants with a worldwide area of operation such as BASF, Bayer Crop-Science, Monsanto and Syngenta. They are concentrating considerable attention on molecular plant biotechnology, which is seen as a future growth factor in agro-industry. The traditional pesticide market, on the other hand has been stagnating for years.

Livestock Breeding:

Modern biotechnology is being employed commercially to introduce novel performance features in productive livestock. The transgenic specimens then display for example different wool characteristics for sheep, or improved milk characteristics in cattle.

Grey/White Biotechnology:

The terms Grey and White Biotechnology have been coined for the application of biotechnological processes in environmental and industrial production contexts. The latter is primarily focused on the production of fine chemicals, in particular technical enzymes.

Technical Enzymes:

Modern biotechnology already dominates the technical enzymes market. They can be found as proteases, lipases, celluloses and amylases for example in modern detergents, where the serve, amongst other purposes as protein and fat solubilizes.

Safety Concerns:

There are a number of safety issues relating to biotechnology products that differ from those raised by low molecular weight products and need to be taken into account when designing the safety evaluation programme for a biotechnology derived pharmaceutical product.

The quality and consistency of the product requires careful control in terms of product identity, potency and purity because of concerns about microbiological safety, impurities arising from the manufacturing process (e.g., host-cell contaminants, endotoxin, residual DNA levels and process chemicals), and the

fidelity of the protein sequence and post-translational modifications during process improvements and scale-up.

The immunogenic nature of heterologous proteins, vectors, cells, tissues and process contaminants must also be considered in the design of the safety evaluation programme and appropriate monitoring for anti-product antibodies, particularly neutralizing antibodies included in toxicity studies to aid interpretation of the findings. For gene transfer products, there are concerns about the distribution and persistence of vector sequences, the potential for expression of vector sequences in non-target cells: tissues and, in particular, the potential for inadvertent gonadal distribution and germ-line integration.

In 1997, the Food and Drug Administration (FDA) became aware that preclinical studies from multiple clinical trial applications indicated evidence of vector DNA in animal gonadal tissues following extra gonadal administration. These positive polymerase chain reaction (PCR) signals were for DNA extracts from whole gonads subsequent to vector administration. The observations involved multiple classes of vectors, formulations and routes of administration.