

Medicines for Mankind

TODAY'S RESEARCH, TOMORROW'S CURES

BIOTECHNOLOGY
PROMISE TO HUMAN
HEALTHCARE

1978 - 2003



EUROPEAN FEDERATION
OF PHARMACEUTICAL INDUSTRIES
AND ASSOCIATIONS

Introduction

Much of the excitement in modern biotechnology of the past 20 years or so has been associated with scientists' increasing ability to control the basic processes of biology. In traditional biotechnologies, such as brewing, dairy production and agriculture, mankind has always harnessed and adapted living organisms. Crops and domestic animals have been selected by farmers for particular traits. The microbes used today in the manufacture of antibiotics have been developed through mutation and selection from earlier, much lower-yielding strains. But increased understanding of basic biology has now enabled researchers to control the introduction of novel traits more precisely.

"The key to every biological problem must finally be sought in the cell, for every living organism is, or at some time has been, a cell". (E.B. Wilson 1925)

The cell is the simplest unit to exhibit life's functions. For the past century, ever more of life's functions have been interpreted in terms of cellular chemistry. As Jacques Loeb argued in his 1912 essay collection, *The Mechanistic Conception of Life*, the cell is like a chemical machine. We now have both the molecular tools and the conceptual frameworks to understand how cells operate. Major milestones are:

- 1943 - DNA is shown to be the genetic material
- 1953 - The double helical structure proposed for DNA by Watson and Crick
- 1966 - DNA's complete genetic code was deciphered

Biotechnology is founded on these key findings and upon an ever-increasing understanding of the mechanisms that maintain living organisms and allow them to reproduce from generation to generation. At the heart of life is deoxyribonucleic acid (DNA), the long, double helix molecule that carries the hereditary genetic instructions necessary to produce organisms. By altering its DNA, an organism can be persuaded to produce more of a particular protein or to produce an altered form of a protein.

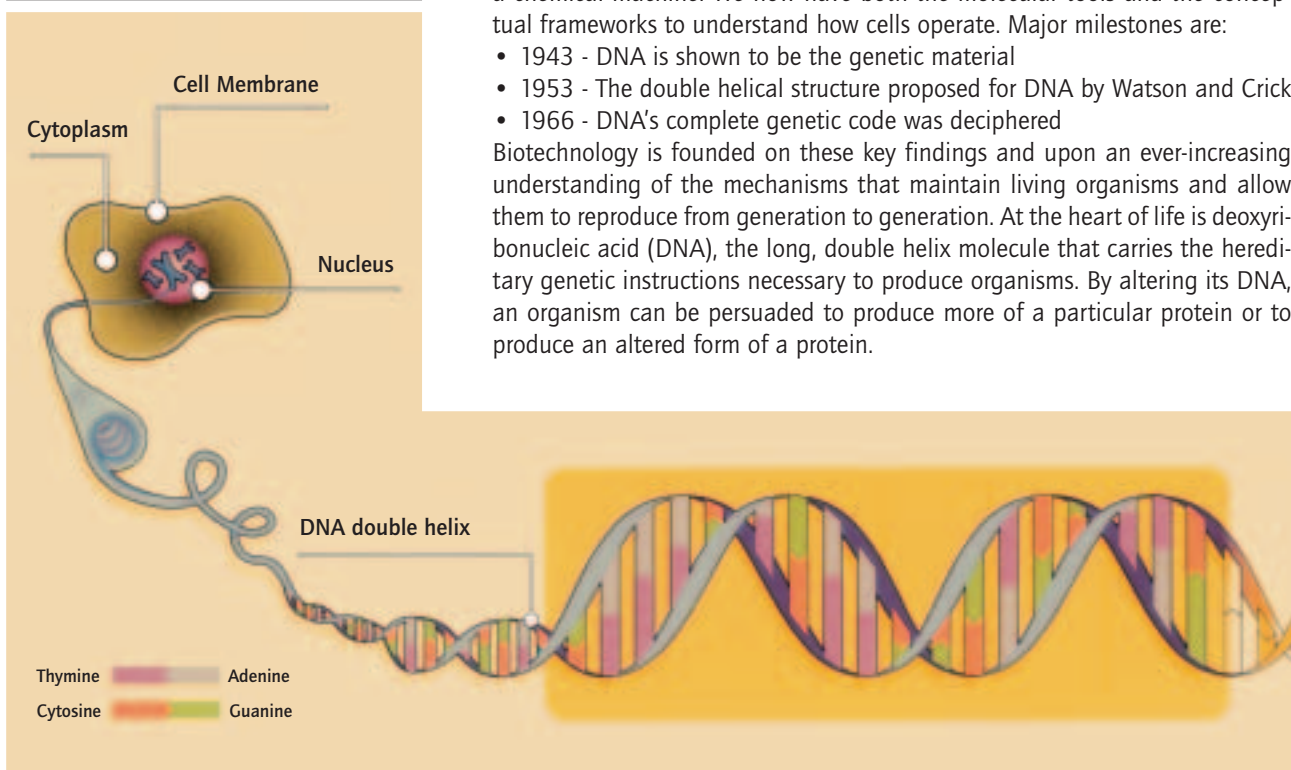


FIGURE 1 DNA double helix

Biotechnology can be defined as the collection of key enabling technologies using biological information and techniques at the molecular level towards the discovery and production of innovative products.

The Technology

DNA – the masterplan of life

The modern revolution in molecular biology has resulted from the ability to manipulate the genetic make-up – i.e., DNA sequences – of a living organism to introduce a new characteristic. The term 'biotechnology' is often used to refer to the techniques of recombinant DNA. It simply refers to the transfer of a gene from one organism into another organism, literally DNA from different sources that has been recombined.

Wholly contained by almost every cell, DNA maps the information necessary to control the cell's chemistry. DNA has two unique properties that differentiate it from all

other molecules: DNA can replicate itself and DNA has the capacity to encode all the genes needed to make the entire diversity of life found on earth.

DNA is a string composed of two strands wound around each other, much like strands in a rope, forming a double helix. Each strand is composed of millions of minute sub-units linked together and called nucleotides. These units of chemical coding are named according to the bases involved: adenine, thymine, cytosine and guanosine, or A,T,C, and G. The nucleotide bases form a simple four-letter alphabet that can code for the 20 amino acids found in proteins. In the language of the genetic code, all words, called codons, for individual amino acids are exactly three bases long. A gene can be thought of a sentence composed entirely of these three-letter words. It is the sequence of these bases in the DNA molecules which determines the biochemistry of cells and physiology of organisms.

The living factory

Because the genetic code is the same among all organisms, it is possible to take a segment of DNA from one source, a human for example, and expect a bacterium to produce the human protein. To accomplish this, the basic tools of genetic engineering are used as summarised in Figure 2:

Individual genes from human DNA can be isolated and inserted into small circular pieces of DNA, called plasmids. Constructed in this way, the recombinant plasmid can be inserted into a bacterial, yeast or cultured animal cell. Once inside the cell, the human gene can be read by the cell's protein-making machinery. Following the multiplication of the engineered host cell in a fermentation tank, the recombinant protein can be found in the cell or in the surrounding medium.

The host cell can be used as a 'living factory' to produce a desired protein product, such as blood clotting factor, or a vaccine.

Genetic engineering is not restricted to microbes. Many different plant and animal species can be made transgenic, that is, new sequences can be introduced into their genome that are stable and are transmitted to the next generation. Transgenic animals can be used for the production of proteins or as disease models enabling scientists to study diseases such as Alzheimer's disease, cancer, atherosclerosis, and to search for new drugs.

Genes and cells as medicines

Other than using genes in the recombinant DNA technology as a tool for production of therapeutic proteins, genes themselves can be used as therapeutic agents. This so-called **gene therapy** is a medical intervention aimed at the transfer of a gene into patients and the expression of the transferred genetic material, resulting in the therapeutic effect. Cells may be modified *ex vivo* for subsequent administration or may be altered *in vivo* by gene therapy products given directly to the subject. This genetic manipulation may be intended to prevent (e.g., DNA vaccines), treat, cure, diagnose or mitigate disease or injuries in humans.

Somatic cell therapy is where living cells, which have been manipulated or processed *ex vivo*, are administered to humans. Manufacture of products for somatic cell therapy involves the *ex vivo* propagation, expansion, selection, or pharmacological treatment of cells, or alteration of their biological characteristics.

Another technology which has created vehement discussions in the public over the past few years is **cloning**. Cloning is an essential process in biotechnology research.

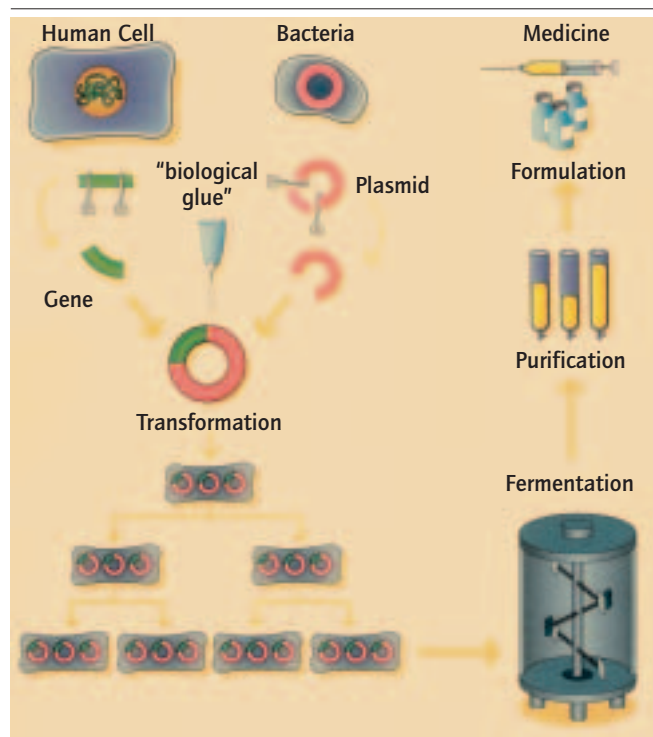


FIGURE 2 Recombinant DNA technique

Cloning is copying. The result of cloning is a clone – a collection of cells that are descendants of a single ancestor. The cloning of human and animal cells and specific DNA fragments (e.g., genes' coding for therapeutic proteins) has been carried out for many years and has provided significant advances in biomedical research. The potential of cloning technology for medical applications has been widened considerably through pioneering experiments leading to the sheep 'Dolly', proving that '*adult DNA cloning*' (also known as '*Cell Nuclear Replacement*' or '*reproductive cloning*') is feasible. In this procedure, the DNA from an ovum is replaced by the DNA from an **adult, differentiated** cell. In the case of 'Dolly', the resulting embryo was allowed to develop into a new animal with DNA identical to the adult from whom the DNA was taken.

The diagnostic fingerprint

Other applications of recombinant DNA technology involve analysing DNA sequences rather than changing them. The biggest breakthrough in modern **diagnostics** is the **Polymerase Chain Reaction (PCR)**. It is an important technique which allows millions of copies of a single DNA molecule to be made in a test tube, thereby providing sufficient quantities of DNA material for analysis. PCR has been called the technique that 'finds a genetic needle in a haystack and than builds a haystack of needles'.

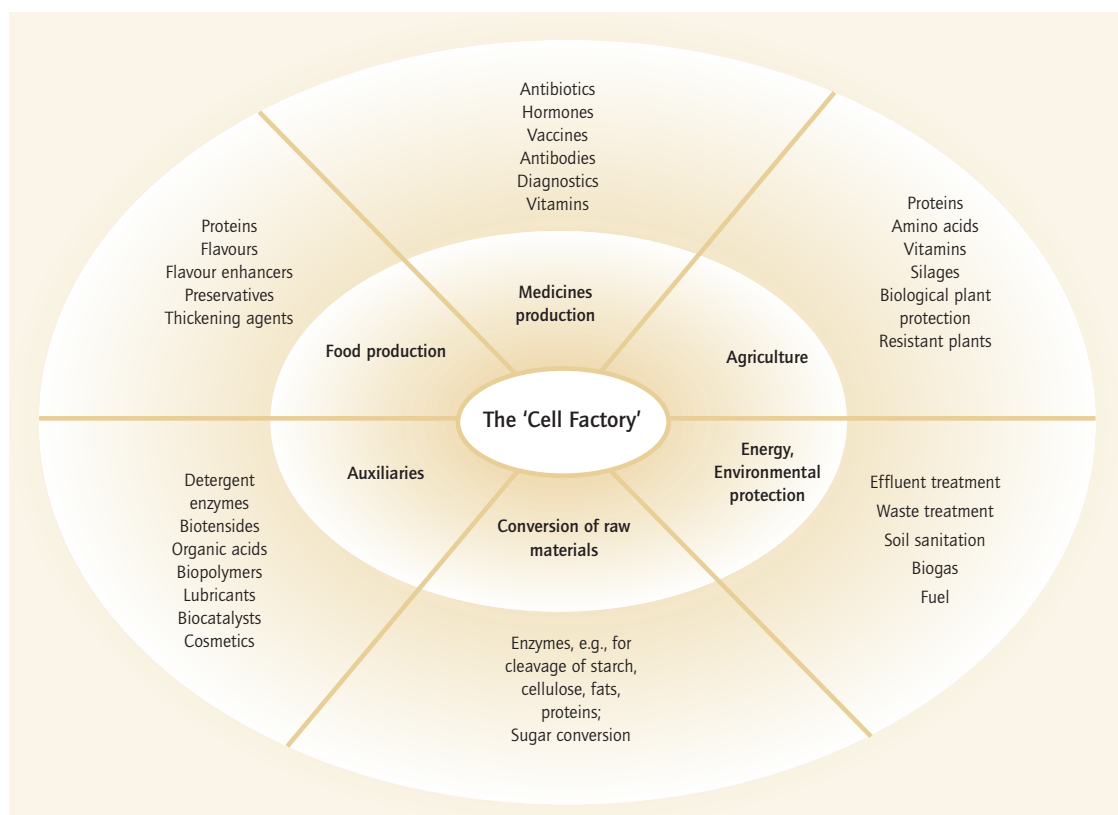
The Achievements

Over the past two decades, biotechnology has played an increasing role in the development of new products and processes in various areas such as medicines, agriculture, food production, and even energy and environmental protection (Figure 3).

Success and societal acceptance of the application of biotechnology vary considerably according to the field in which it is used. According to *Eurobarometer 58.0*, a report to the EC Directorate General for Research of March 2003, the medical application of biotechnology wins greatest support in Europe. The reason lies in the great promise to human healthcare based on the fact that biotechnology:

- Has enabled the development of otherwise unavailable and novel biological medicines;

FIGURE 3
Application of
Biotechnology



- Has provided new efficient methods for the large-scale production of existing substances;
- Is the basis for novel, highly sensitive and specific diagnostic tests;
- Is the basis for the development of new and often inherently safer vaccines; and
- Is a major basis for new fundamental understanding of normal and disease processes.

Access to human therapeutic proteins

Biotechnology offers the opportunity to use the body's own molecules as medicines. There are many examples of diseases caused by the absence or the impaired functioning of proteins. The synthesis and purification of these human proteins from cloned genes is an important medical application of genetic manipulation, and the majority of **biopharmaceuticals** marketed to date (Figure 4) are recombinant therapeutic protein drugs. (*Biopharmaceuticals can be defined as biological substances, or derivatives of biological substances, that closely resemble their natural counterparts, but are made through biotechnological processes rather than isolated from biological materials or created through classical organic synthesis techniques, as are other pharmaceuticals.*)

FIGURE 4 Biopharmaceuticals

Product Category	Diseases to be treated (non exhaustive)
Hormones	Diabetes; Growth deficiency in children
Interferons	Kaposi's sarcoma; Multiple sclerosis
Interleukins	Renal cell carcinoma
Colony stimulating factor	Autologous bone marrow transplantation; Chemotherapy-induced neutropenia
Erythropoietin	Anemia associated with chronic renal failure
Tissue plasmin activator	Acute myocardial infarction; Acute pulmonary embolism
Clotting Factors	Haemophilia
Anticoagulants	Heparin-induced thrombocytopenia
Soluble receptors	Renal transplant rejection
Monoclonal Antibodies	Acute kidney transplant rejection; Crohn's disease; Breast cancer
Vaccines	Hepatitis

Before recombinant protein DNA technology was available, the only source of these protein drugs was animal or human tissues or body fluids such as blood, urine or placenta. The use of biotechnology has overcome limitations in the supply of starting material from natural sources. For example, protein replacement is the only existing therapy for the treatment of Gaucher disease, a seriously debilitating and sometimes fatal genetic disorder. Until 1994, a modified form of the protein was prepared from human placental tissue, with the problem that the limited availability of this tissue restricted the amount of medicine that could be produced. Other examples are:

- Recombinant hematopoietic growth factor is now used to boost the production of both red and white blood cells for the treatment of anaemia and neutropenia;
- Cytokines, key factors of the immune system are produced recombinantly and are used in the treatment of cancer, multiple sclerosis, rheumatoid arthritis, and many other deadly and disabling diseases; and
- Antibodies are proteins that provide immunity to infection, or slow disease progression. These proteins, which the body normally produces in very small quantities, can now be manufactured in larger, distributable quantities.

Since the first recombinant medicine was marketed in 1982, 95 biotechnology medicines have been approved and made available to patients, and the share of biotechnology medicines in novel products is continuously increasing. In 2002, out of the 25 medicinal products approved by EMEA, the European Agency for the Evaluation of

Medicinal Products, 9 are biologicals. Similar figures (9 out of 26) have been reported from the US FDA for 2002.

Using recombinant DNA technology to produce human proteins enables us not only to provide for the quantities required but also to reduce the possibility of adverse effects, e.g., Creutzfeld-Jakob disease, Hepatitis B or HIV, resulting from impurities in the proteins isolated from a natural source.

Recombinant techniques have become the most attractive and useful route to the development and production of **vaccines**. In traditional vaccine manufacture, living vaccines or attenuated viruses are produced to stimulate the recipient's own immunity to the organism causing the infection. However, the difficulties of mass-producing vaccines from plasma, safety considerations, high production costs and time-consuming production processes prompted researchers to come up with a genetically engineered alternative. The first human recombinant vaccine was introduced to fight Hepatitis B, one of the most common infectious diseases known. Pertussis vaccines and others followed, and a number of pathogens, such as HIV, Papillomavirus and *Helicobacter pylori* are now the target for 'therapeutic vaccines', which can be used not only for prevention of diseases, but also to treat them.

Modern diagnosis

Treatment and prevention of diseases depend considerably on a precise diagnosis. A wide variety of **diagnostic** tools involving biotechnology are available. The **Polymerase Chain Reaction (PCR)** has opened a new area in medical diagnostics. Among the many important applications for PCR are archaeology, criminology, paternity testing and biology research. One of its most impressive research uses is in the Human Genome Project, where it is helping to define all the genes contained on our chromosomes. Any disease or disorder that is characterized by the presence of foreign or mutated DNA can be diagnosed using PCR.

Many serious infections are caused by a small number of pathogens – as few as 10 per millilitre in a sample of body fluid. Unfortunately, tests that directly detect pathogens typically require up to 10,000 microorganisms per millilitre. To culture (or grow) that many pathogens is difficult, time-consuming, costly and sometimes simply impossible. With PCR, diagnostic laboratories can now produce detectable quantities of DNA in a single work shift using specimens that contain as few as 1 to 10 copies of a virus or bacterium. In the case of HIV, the ability to obtain a speedy diagnosis is vital to containing the spread of infection and beginning therapy. Until PCR, HIV infection could be determined with the standard procedures only 2-3 months after the exposure to the virus. During that time, the patient will not be receiving treatment and may unwittingly be spreading the virus to others. By speeding the diagnosis of HIV, PCR can help change these realities. PCR diagnostics similar to those available for HIV are also available for early detection of infection with hepatitis C virus, *mycobacterium tuberculosis*, *chlamydiae*, and others.

Because it can also distinguish normal from abnormal (or mutated) DNA, PCR enables doctors to offer more expert screening of people with a family history of genetic diseases. Some 4,000 diseases of genetic origin have been identified and genetic defects that are responsible for many signs and symptoms of disease can now be detected. Examples of such diseases are: cystic fibrosis, duchenne muscular dystrophy, Huntington's disease, phenylketonuria, *retinitis pigmentosa*, and others.

PCR's ability to 'type' (or classify) tissue is expected to be of great benefit to organ and bone marrow transplantation where it can help to make the best possible matches between donors and recipients.

Biotechnology – an essential research tool

The preparation and supply of the many new life-saving biopharmaceuticals and modern diagnostic tools for the benefit of millions of patients is the most obvious achievement of biotechnology. In addition to that, biotechnology as a **research tool** has

opened new avenues to biomedical research. In providing better and greater fundamental knowledge of complex biological processes, it is leading to the discovery and development of new 'conventional' medicines, i.e., small chemical molecules. Modern biomedical and pharmaceutical research, whether in academia or in the pharmaceutical industry, would be unthinkable without biotechnology. The pharmaceutical industry will soon be driven by biotechnology, in much the same way that the electronics industry is now driven by microchip technology.

Biotechnology tools enhance the probability and speed of identifying novel drug candidates. They contribute to drug discovery through:

- Novelty and diversity of drug targets and compounds;
- Selectivity in target definition;
- Optimisation of safety and efficacy profile; and
- Cost-effective processes.

A key element in this context is the understanding of DNA structure and the information on the make-up of individual genes.

One impressive example of the power of gene-based approaches is the discovery of the new AIDS therapies. Scientists deciphered the genome of the AIDS virus in 1983, revealing for the first time the existence of a range of new molecular targets. One of these, the HIV protease, an essential component of the virus and completely unknown a decade ago, has been the target for the development of a range of drugs which have an important role in the treatment of AIDS. Without biotechnology, such advances would not have been possible.

Likewise of great importance is the knowledge of the human genome for the understanding of pathophysiology and for development of new medicines. The extraordinary breakthrough of the **Human Genome Project** was possible through the development of automated techniques and progress in information technology (bioinformatics) that allow many thousands of base pairs of sequence to be read in a single day. Thanks to this massive project, on a scale unparalleled in the history of biology, scientists now know the chemical sequence of the DNA that makes up the 35,000 human genes.

The completion of the human genome sequence certainly marked an important step in the history of biology. For the first time, we will be able to study in detail our hereditary blueprint in the material that is the prerequisite to the existence of all forms of life on earth.

The mapping of the human genome has raised expectations that the benefit to medicine, in general, and the search for innovative pharmaceutical therapies to combat disease, in particular, will be profound. It is also expected to lead to a significant reduction in the time taken to develop these drugs. This has led to a change in paradigm in the approach to drug discovery. The complete sequence of a gene must be known if its function is to be studied in detail. It is now possible to list the biological attributes of genes that would be used to facilitate the drug discovery:

- The complete genomic sequence;
- The expression pattern in normal development and adult tissue, and alterations found in disease;

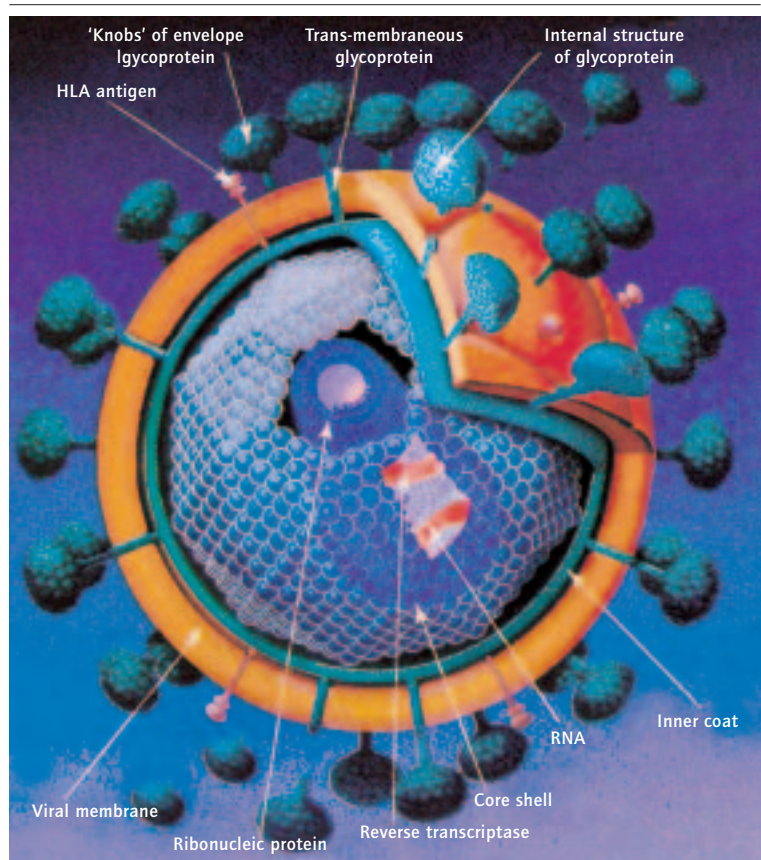


FIGURE 5 Structure of a Human Immunodeficiency Virus (HIV)

- Sequence variation found in healthy individuals and variations found in individuals afflicted by disease; and
- Animal models with specific alterations.

All this enables the pharmaceutical industry to develop medicines which will be the medical breakthroughs of the new millennium. The boom in R&D productivity driven by innovations in technology already finds expression in the high number of 371 biotechnology medicines currently in preclinical or clinical development according to a survey by the Pharmaceutical Research and Manufacturers of America (PhRMA, 2002). These biopharmaceuticals offer hope of new treatments for more than 200 diseases, including 178 new medicines for cancer, 47 for infectious diseases, 26 for autoimmune diseases, 22 for neurological disorders, and 21 for HIV/AIDS and related conditions.

Biotechnology – an economic driver

Addressing the achievements of biotechnology, one should not forget to mention its great **economic impact** and the contribution to employment. Biotechnology means major opportunities for economic gain by companies that exploit the advances it offers. The opportunities are so great that today thousands of start-up companies are scrambling to take advantage of all the discoveries. Some biotech companies have even grown to global players competing with the big established companies.

Outlook

Biotechnology, together with computer technology and advanced engineering technology, has enabled the pharmaceutical industry to develop and produce medicines which were not available before, such as treatments for rare (orphan) diseases.

The use of transgenic animals will open new vistas for the production of special human proteins for therapeutic use. One example is alpha-1-antitrypsin, produced in the milk of transgenic goats, which is being tested in clinical trials for the treatment of cystic fibrosis and emphysema.

New science for new and better therapies

The information from the Human Genome Project is already beginning to revolutionise the way we look at human disease and has opened the door for new types of medicines and therapeutic approaches. Current drug therapy is based on less than 500 molecular targets. Through **genomics** – the study of the structure and function of genes and their role in health and disease states – the number of gene products that may be relevant to the pathophysiology of disease will generate 5,000 to 10,000 molecular drug discovery targets. Genome knowledge opens huge prospects for treating both the rare disorders known as ‘Mendelian diseases’, and also some very common health problems like cancer, heart disease, Alzheimer’s disease, and many more (Figure 5). To convert this huge potential into new therapies, diagnostics and vaccines for the patient will be a big challenge to the pharmaceutical industry. The way we carry out research is already changing. Networking and knowledge management to cope with the breathtaking speed with which new technologies evolve need careful attention.

The new science of **proteomics** being developed for studying complex mixtures of expressed proteins is an example of the new research approaches. Because the spectrum of expressed proteins within a cell determines its biology, such comprehensive descriptions will provide the basis for understanding precisely why, for example, brain cells differ from kidney cells. They will identify biological markers characteristic of disease states, leading to techniques for early identification. They will help classify cancers into distinct subtypes, making it possible to know the tumor’s lineage, the nature of the genetic mutations that led to its appearance and, in the long run, whether it will respond to a particular therapy.

Therapeutic cloning or ‘cell nuclear replacement’ is not aimed at creating a new mammal in itself (as in the case of the sheep ‘Dolly’), but at growing the manipulat-

ed ovum into a very early embryonic stage. The aim is to isolate 'stem cells' from such human embryos. The therapeutic potential of these embryonic stem cells is based on their 'pluripotent' nature, i.e., their ability to develop into a great variety of different cell and tissue types.

The use of such stem cells is expected to revolutionise the treatment options for a wide range of serious conditions and degenerative diseases. In multiple sclerosis, for instance, stem cell technology could be used to regenerate nerve cells damaged by the disease. In particular, it could make possible an unlimited supply of tailor-made tissue or organs for transplants or grafts. The risk of transplant rejection would be eliminated, and transplanted patients would be spared the long and often desperate wait for a donor.

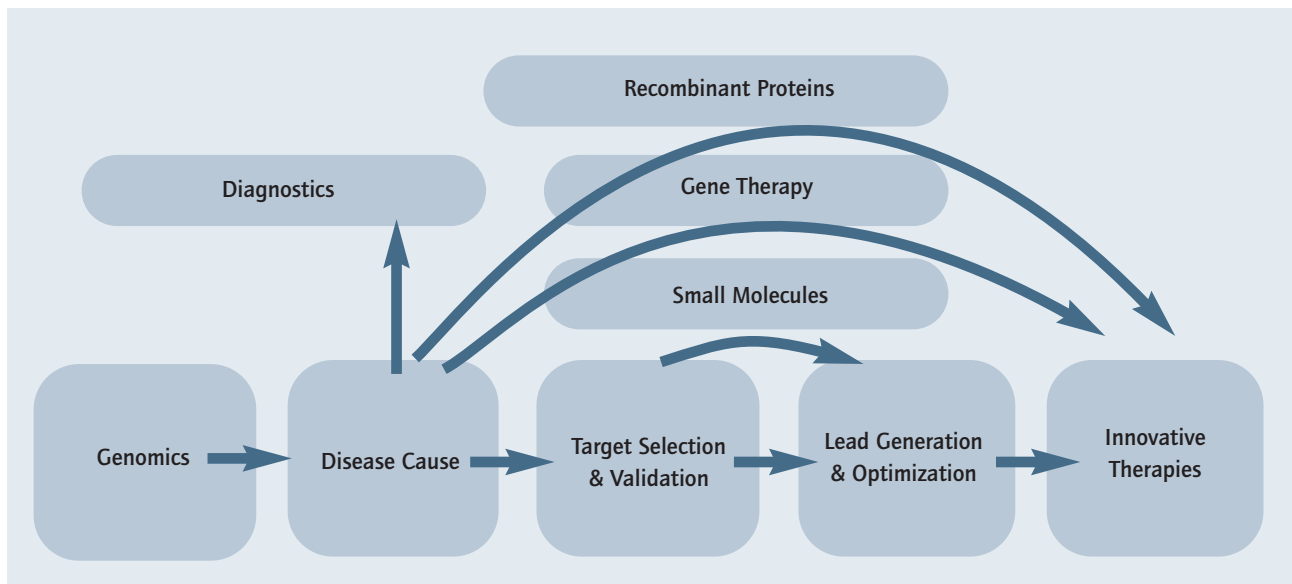


FIGURE 6 Genomics – a key driver to enhance innovation & productivity

Gene therapy is potentially applicable both to single-gene disorders – caused by a single absent or malfunctional gene – and to multifactorial diseases – where environmental factors, as well as genes, contribute to susceptibility. It is still a very young technology and, as with any new therapeutic approach, its success will depend on the efficacy and safety of its methods. Despite many significant achievements, there are still obstacles to the development of effective clinical products. Whereas some disappointing clinical results have reduced interest in certain areas, there have also been novel and exciting developments. It is too early to answer conclusively which applications or diseases will be most suited to gene therapy, but ongoing clinical trials suggest that, for many diseases, gene therapy may prove to be the therapy of choice in the 21st century.

Tailor-made medicines

Biotechnology is not only changing the way we carry out medical and pharmaceutical research, but changes are also likely to occur in the way drug development is conducted.

Pharmacogenetics, the science of understanding the correlation between an individual patient's genotype and their response to drug therapy, i.e., safety and efficacy, is a new tool for drug development. It will have an impact on clinical trials and on prescribing and post-marketing surveillance. Today a typical drug development programme usually proceeds on the broad assumption that patients are homogenous groups with little inter-individual variability. However, all patients do not respond to the same medicines in the same way, both in terms of efficacy and adverse reactions. Knowledge of the genetic differences that explain these individual characteristics is critical for the development of specific therapeutics. Genetic testing carried out in pharmacogenetics is already beginning to be used in some areas, such as oncology,

as a tool to aid therapeutic decisions. It will optimise treatment to individual patients or patient groups and it should also provide a more effective use of healthcare resources.

All these new techniques and approaches and others already advanced, such as **tissue engineering**, **xenotransplantation**, **nanobiotechnology**, will offer solutions to many problems for which treatments have long eluded us.

Clinical interest in **xenotransplantation**, the transplantation of live cells, tissues or organs from non-humans to humans, is prompted by the shortage of human donor organs for transplantation. Xenotransplantation can take a number of forms:

- Transplantation of solid animal organs (e.g., heart, liver); or
- Cell therapies, such as the transplantation of pig neural cells, pancreatic islet cells, etc.



There are still scientific hurdles and safety issues. However, recent advances in understanding the mechanisms of transplant organ rejection have brought us to a stage where it is reasonable to consider that organs from other species, probably pigs, may soon be used as an alternative to human tissues. First human studies are ongoing in a few diseases with cells obtained from xenogeneic origins (e.g., foetal dopaminergic neurons obtained from pigs applied in Parkinson's and Huntingtons's disease patients).

Nanobiotechnology refers to the ability to create and manipulate biological and biochemical materials, devices, and systems at atomic and molecular levels (10^{-9} m). Potential applications include systems for improved drug and gene delivery; biocompatible, high-performance materials for implants; and nanoscale sensors to detect biological agents and disease.

Social acceptance of biotechnology

Scientific progress leading to many new approaches in healthcare raises a variety of **ethical, moral and social issues** despite the potential benefits. As always, revolutionary discoveries give rise to fears. Particularly in Europe issues such as the use of transgenic animals, cloning, genetic testing and the legal protection of biotechnological inventions are being intensively discussed by scientists, politicians, regulators and the general public.

For instance, the information produced by genetic tests, while very valuable for medical diagnosis and treatment, may also be used out of context in ways that are contrary to the interests of the patient, e.g., by insurers, employers or government agencies. Policies protecting confidentiality in research are crucial both to guard individual privacy and to promote the advancement of science. Science is expanding at a breathtaking pace, and the overwhelming amount of new information puts governments under increasing pressure to pass legislation on what genetic information should be protected, who will have access to it, and how it may be used.

Pharmaceutical research carried out in industry is determined by a medical need for a new or better medicine, and by safety, efficacy and economic criteria. However, the therapeutic concept and the approaches in research and clinical development have to be in agreement with the ethical, legal and social environment in a society. Therefore,

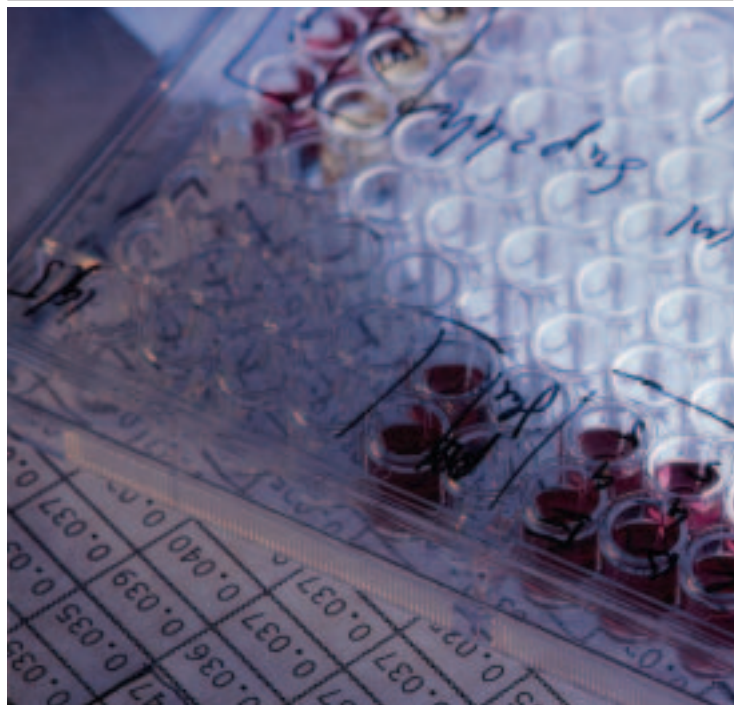
it is essential that there be a common understanding of social and ethical issues and that the regulatory requirements for the development of new medicinal products and therapeutic approaches are practicable and in line with the new scientific knowledge. Ambiguity and controversial positions are highly detrimental to pharmaceutical companies' decisions on investment in new R&D operations and where they should be sited which, in turn, has implications on the European competitiveness in biomedical research and the pharmaceutical industry.

Conclusions

Biotechnology has revolutionised medicine and will continue to contribute to better ways to prevent and to treat diseases and thereby further improve quality of life and extend life-expectancy.

Society has to face the fact that the advances in medical science are increasing the number of possible treatments, and public expectations are steadily increasing, which inevitably adds to the health bill. The costs of scientific research are inflating and there is heightened concern over drug safety, which makes the development of new medicines increasingly expensive. Furthermore, medical science is beginning to subdivide diseases into separate categories, each of which needs a separate treatment. It means a range of medicines for smaller groups of people, rather than a single medicine for a larger group which, in turn, means that development costs increase but the overall market does not.

In a world where health services have finite resources but face a potentially infinite demand, this is a difficult situation. This is not a popular topic for politicians, doctors or patients and not for the pharmaceutical industry, but it is one that must be addressed.





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