Biotechnology
applications in industry

Regional Activity Centre for Cleaner Production (RAC/CP)
Mediterranean Action Plan

UNEP

MAP

Regional Activity Centre for Cleaner Production

Ministry of the Environment
Spain

Government of Catalonia
Ministry of the Environment

If you consider that any point of this study may be improved upon or is erroneous, we would appreciate your comments.

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INTRODUCTION

The Regional Activity Centre for Cleaner Production (RAC/CP) of the Mediterranean Action Plan (MAP) has carried out this study on biotechnology applications in industry in the MAP countries in order to define the basic concepts of biotechnology, show the situation and the degree of advancement in these techniques in different countries of the Mediterranean region, and to present some examples of application on an industrial scale.

This study was principally based on the bibliographic research of databases obtained on the Internet and at university libraries and information from databases obtained through European biotechnology societies. Likewise, the experience that the work group of the Polytechnic University of Catalonia has gained thanks to its research into cleaner production applied to industry, pharmacology and molecular biology.

The information which is presented concerning the different countries was compiled by the team of experts at the Polytechnic University of Catalonia, which has carried out the study and, furthermore, has been contrasted and complemented with the information provided by the respective countries' national focal points[1].

Biotechnology is a multidisciplinary science which includes different techniques and processes, and is today perhaps, together with information sciences, the most state-of-the-art emerging technology, and indeed the technology which promises the brightest future. Moreover, this situation has been accelerated by the major breakthroughs experienced in the field of molecular biology in recent years, which has opened the door to obtaining new organisms and designer proteins.

Faced with increasing pollution of the planet, biotechnology is considered as being a solution in many fields of pollution prevention, the treatment of waste and the new technologies which pollute less.

Regarding the contents of the study, it consists of five main chapters:

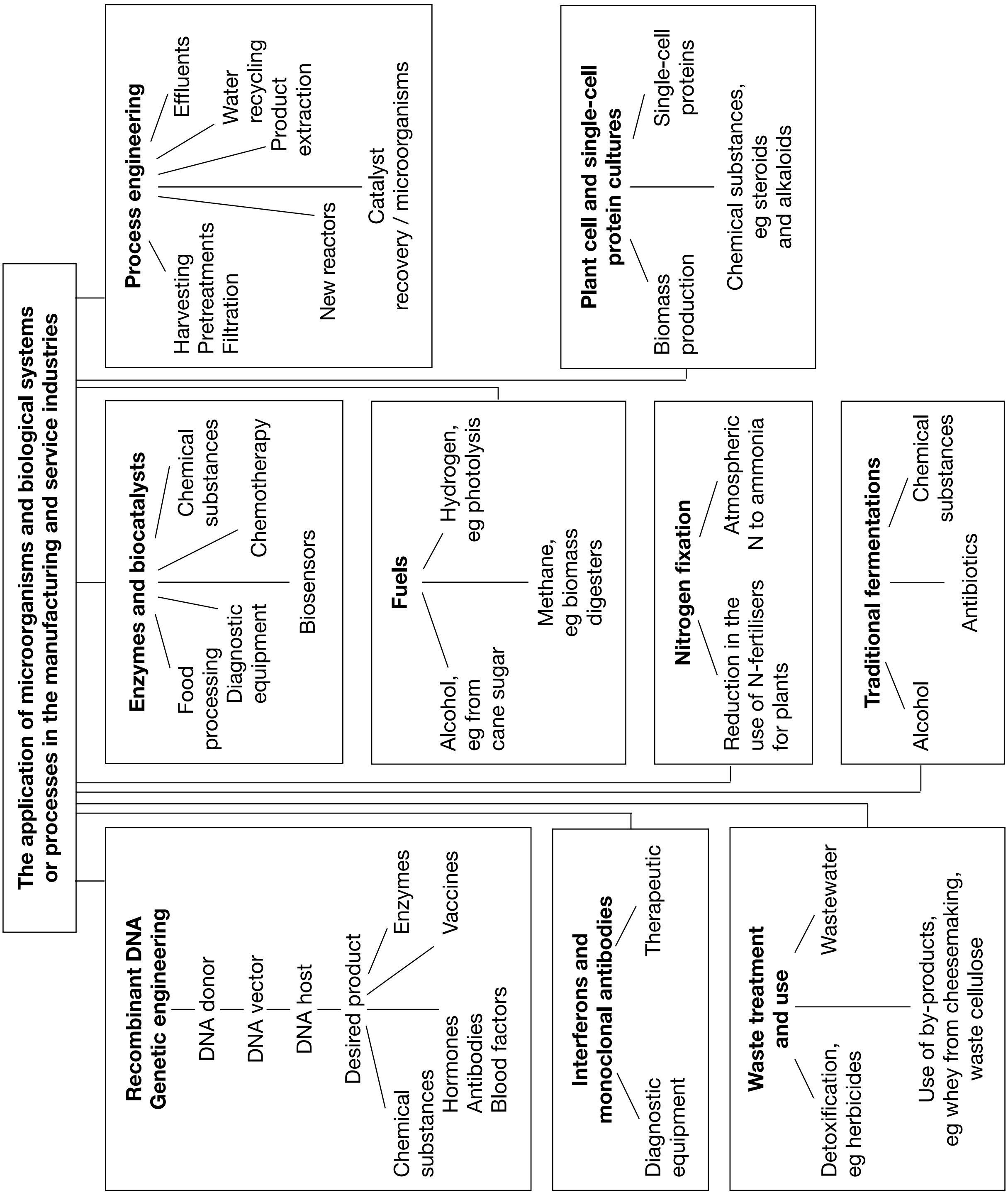
1. Chapter one presents the concept of biotechnology: its evolution and development, the main technological areas as well as the industrial and geographical scopes of the application of these techniques.
2. Chapter two shows some of the main applications in the industrial sector.
3. Chapter three presents different case studies, which have already been used on an industrial scale in sectors and processes such as winemaking, wastewater treatment, the food industry, etc.
4. Chapter four describes the situation and application of biotechnology in different countries of the Mediterranean basin, concentrating especially on the institutions that are researching into and applying these techniques and how they are promoted.
5. Finally, chapter five deals with the trends in and possible future development of biotechnology.

[1] Barring information supplied on France and Greece.

This paper was written taking two visions into account: the definition of biotechnology and its technological areas (vertical vision) and the description of the industrial sectors that already apply or may apply one or several areas of biotechnology in the future (horizontal vision).

Economic data is presented in this document in euros. Conversion used when necessary is the following: 1 euro = 0.9921 US$ = 0.6395 £ = 166.386 pesetas = 6.5596 French francs = 4.6056 new shekels.

Figure 1
AREAS OF INTEREST IN BIOTECHNOLOGY



1. BIOTECHNOLOGY

In this chapter we review the concept of biotechnology and make some general considerations.

1.1. WHAT IS BIOTECHNOLOGY?

It is a difficult task to establish an unequivocal definition of biotechnology given that it encompasses different scientific and production activities. Moreover, biotechnology covers a broad range of concepts, from technological to scientific. However, the lack of an agreed definition has not halted the advance of biotechnological development.

Some definitions of biotechnology which appear in the bibliography are:

> "Biotechnology is a set of powerful tools that uses live organisms (or part of these organisms) in order to obtain or modify products, improve plant and animal species or to develop micro-organisms for specific uses"[2].
>
> "Biotechnology is the technique of manipulating life forms (organisms) in order to obtain products that are useful for humanity"[3].
>
> "Biotechnology is the application of the principles of science and engineering to the processing of materials by means of biological agents in order to obtain products and services"[4].
>
> "Biotechnology is the integration of natural science and engineering in order to manage to apply organisms and cells —or parts thereof— as well as molecular analogues in the production of goods and services"[5].
>
> "Biotechnology is the industrial use of live organisms or biological techniques developed in basic research. Biotechnological products include: antibiotics, insulin, interferon, recombinant DNA and monoclonal antibodies. Biotechnological techniques include: genetic engineering, cell cultures, tissue cultures, bioprocesses, protein engineering, biocatalysis, biosensors and bioengineering"[6].
>
> "Biotechnology is not one sole technology, rather it groups together several techniques whose common denominator is the manipulation of living cells and their molecules, and the practical application of these processes to improve life"[7].

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[2] Washington Biotechnology and Medical Technology Online (http://www.wabio.org/definition_biotech.htm).
[3] Web site: http://www.miracosta.cc.ca.us/mcbc/pw/b2bglossary.htm
[4] Matthew Herwig (http://www.engr.umbc.edu/~mherwi1/proj1.html).
[5] EFB General Assembly, 1989 (http://www.eurodoctor.it/biotech.html).
[6] *The Biotech Life Sciences Dictionary* (http://www.eurodoctor.it/biotech.html).
[7] North Carolina Biotechnology Center (http://www.ncbiotech.org/).

> "In general terms, biotechnology is the use of biological processes in order to obtain useful products, which include modified organisms, substances and apparatus"[8].

> "Biotechnology is the name given to those biological processes that produce beneficial substances for agriculture, industry, medicine and the environment"[9].

According to the United States Government Press Office's Office of Technology Assessment, there are two definitions of biotechnology. One broad definition encompasses old and new biotechnology[10]:

> "Biotechnology refers to all techniques that use living organisms (or part thereof) in order to create or develop micro-organisms for specific uses."

The other, more restricted definition is specifically applied to modern biotechnology:

> "Biotechnology is the industry that uses recombinant DNA, cell fusion and new bioprocess techniques".

> "Biotechnology is the application of science and engineering to the direct or indirect use of living organisms, parts of organisms or products of living organisms, in their natural or modified state"[11].

The OECD (Organisation for Economic Co-operation and Development) describes biotechnology as:

> "The application of science and technology to both living organisms and parts thereof, products and molecules in order to modify living or non-living matter to produce knowledge, goods and services."

To this end, other definitions exist:

> "Biotechnology simply consists of the use of micro-organisms and vegetable and animal cells to produce materials, such as foods, medicines and chemical products which are useful to mankind"[12].

> "Biotechnology is the use of living organisms or compounds obtained from living organisms in order to obtain products which are valuable to mankind"[13].

The FAO (United Nations' Food and Agriculture Organisation) offers two complementary definitions of biotechnology[14]:

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[8] Bioindustry Association (http://www.bioindustry.org).
[9] Canadian Food Inspection Agency (www.cfia-acia.agr.ca).
[10] Office of Technology Assessment Publications (OTA Publications). *Biotechnology in Global Economy.* Congress of the United States, 1991.
[11] The Biotechnology Gateway. Canada Industry (http://strategis.ic.gc.ca/SSG/bo01074e.html).
[12] El Centro Bioinfo (http://www.porquebiotecnologia.com.ar/doc/biotecnologia/biotec.asp).
[13] Infoagro (http://www.infoagro.com/semillas_viveros/semillas/biotecnologia.asp).
[14] The United Nations' Food and Agriculture Organisation (FAO) http://www.fao.org/DOCREP/003/X3910E/X3910E00.htm).

> “The use of biological processes or living organisms for the production of materials and services for the benefit of mankind. Biotechnology includes the use of techniques that increase the economic value of plants and animals and develop micro-organisms to act in the environment”.

> “Biotechnology implies the scientifically-based manipulation of living organisms, especially on a genetic scale, to produce new products such as hormones, vaccines, monoclonal antibodies, etc.”.

Some biotechnologists define biotechnology as being “a technology that applies the potential of living beings and the possibility of their selective, programmed modification to obtaining products, goods and services”. Therefore, biotechnology encompasses the fundaments of a great many disciplines, ranging from classical biology (taxonomy), to bioengineering, through genetic engineering, microbiology, biochemistry, cellular and molecular biology, immunology, etc. (Muñoz, 1994).

According to J. D. Bu’lock (1991), biotechnology “is the controlled, deliberate application of simple biological agents —living or dead cells, cell components— in technical operations for the manufacture of products or to obtain services”.

Therefore, the word biotechnology is sometimes used in too restricted a way, such as genetic manipulation and molecular biology applied to obtaining useful goods and services. And, in a broad sense, biotechnology encompasses all operations of applied biology, from agriculture to culinary sciences.

The distant beginnings of biotechnology are to be found in primitive societies with the making of bread, cheese, wine, beer, etc. Beekeeping and livestock rearing may also be considered as precursors of biotechnology. However, the use of the word biotechnology in the United States —one of the most advanced countries in this field— has come to mean a whole industrial sector devoted to creating, developing and marketing a range of products obtained by means of genetic manipulation, molecular biology or through the controlled, guided application of micro-organisms or parts thereof.

If we look at a more industrial application, we may define the fields of biotechnology in relation with the products obtained.

- The production of microbial biomass for animal food.
- The microbial production of chemical substances, such as citric acid, glutamic acid, aminoacids, etc.
- The enzymatic production of special chemical substances, such as certain optical isomers, etc.
- The microbial or enzymatic production of antibiotics and vitamins.
- The large-scale production of chemical substances previously produced from crude oil, such as ethanol, butanol, acetone, acetic acid, etc.
- Production, based on animal or vegetable cells or the cells of genetically modified micro-organisms, of antigens, antibodies, therapeutic and diagnostic agents that were previously manufactured from superior organisms.

- Products for agriculture and livestock. This method means the improvement of plant and animal species through genetic engineering and is far quicker and effective than the methods used to date (cuttings or the selection and crossing of species).
- Products for the food industry, for example: enzymes, food coadjuvants and, above all, greater knowledge of the processes of fermentation which have always been used with the possibility of better selecting the micro-organisms and even genetically improving them.
- Cleaner, or less pollutant technologies. The obtaining of environmentally risk-free —or minimal risk— technology, as a result of the application of the different areas of biotechnology, may also be considered as a product obtained from biotechnology and be applicable to different industrial sectors.

If we look at the type of process, we obtain another distribution of the fields or areas of biotechnology:

- Recombinant DNA (genetic engineering). This technique is the basis of the processes for obtaining enzymes, hormones, antibodies, vaccines, etc.
- The cultivation of vegetable cells and unicellular proteins. This technique is used in the production of chemical substances such as steroids, alkaloids, unicellular proteins for the production of biomass, etc.
- Industrial fermentation. This is an ancient technique, but nowadays, we are able to control it and even steer it in the direction that most interests us. By means of fermentation we obtain foods, antibiotics and chemical products.
- Biocatalysis. This technique is becoming more common and has a broad range of applications; for example, with biocatalysts, food and chemical substances can be obtained. Biosensors and some diagnostic equipment also use biocatalysts. Furthermore, nowadays biocatalysts are applied in order to achieve cleaner technology in sectors such as the textiles, paper and tanning industries, etc.
- Bioremediation. Biotechnology is increasingly applied in the treatment and reuse of waste. In fact, it is the field that presents the broadest range of applications. Thus, biotechnological methods are used to detoxify land polluted by herbicides, in the treatment of wastewater, in recovering industrial waste —for example, whey from cheese-making or cellulose waste—, etc.
- Process engineering. An industry has developed around biotechnological applications that applies chemical engineering methods to biotechnological processes. For example, we find process engineering in the filtering and pre-treatment of effluents, the recycling of water, the extraction of products, the recovery of catalysts and microorganisms, etc.

In short, a practical definition of biotechnology is quite broad indeed and, moreover, changes with time due to the rapid development of new techniques in the field and new discoveries in molecular biology, which constantly open up new perspectives.

The applications of biotechnology are quite diverse and their advantages so obvious that in one way or another, industries are already applying them in their production processes. Some industrial sectors that have implemented biotechnological processes are listed below:

- agriculture,
- livestock,

• aquiculture,
• silviculture,
• pharmacy,
• diagnostics,
• fine chemistry,
• forensic chemistry,
• food,
• soaps and detergents,
• textiles,
• paper,
• bioremediation.

Biotechnology has meant that these sectors can make new or better products, often saving time and energy, in a more environmentally friendly way.

Important advances in health issues have been achieved through biotechnology —for example, new medicines—, new methods for the large-scale production of medicines or more accurate diagnoses for illnesses such as aids. In other areas, biotechnology concentrates on the development of less pollutant processes, consuming less energy and the possibility of recycling natural resources, providing a sustainable base for technological development.

From all the above definitions, it can be deduced that there are two aspects to biotechnology, one on a molecular scale and the other more applied. Nevertheless, they are neither independent nor juxtaposed, rather they are two consecutive, highly interrelated aspects.

It may be concluded that modern biotechnology implies, first, some scientific knowledge of molecular biology, DNA, techniques of manipulation on a molecular scale, as well as of metabolic mechanisms and DNA replication and of the transcription of proteins. This opens up the way for the manipulation of living organisms in order to obtain specific benefits that are applicable to production or remediation.

On the other hand, it may also be deduced from the previous set of definitions that biotechnology is a multidisciplinary field in which science and technology coexist. Among the sciences encompassed by biotechnology we can name biology, botany, molecular biology, genetics, immunology, biochemistry or enzymology. Among the technologies, genetic engineering, fermentation, biocatalysis and process engineering must be considered.

The common denominator of all these definitions of biotechnology is that the difference between biotechnology and other technologies applied to industry is the use of living beings or parts thereof to obtain products that benefit mankind. Therefore, obtaining milk from cows at a livestock farm is biotechnology. However, biotechnology is currently understood as being the application of techniques of genetic manipulation in order to modify organisms that may be used to obtain specific products or services. That is, the obtaining, if it may be said in this way, of a designer organism with predetermined features.

We are now in a position to understand why biotechnology has, in recent years, undergone such important development. Principally, this has been due to advances in molecular biology and also to the latest discoveries concerning genetics.

This has opened the field to multiple industrial applications that were previously unthinkable.

Biotechnological industry can be divided into two major fields: the industry that produces manipulated organisms, or part thereof, and the industry that uses these organisms, or part thereof, to obtain products or services. In this study, we concentrate on the latter, industry that applies microorganisms or part thereof —principally enzymes— to obtain goods and services; and within this, in those industries that use this technology in order to improve the yield of their facilities in order to take better advantage of energy and raw materials or to treat the waste produced more ecologically.

1.2. BACKGROUND

The Background to biotechnology is modern biology. The latter has undergone a great advancement in the techniques of the manipulation of complex organisms and has improved the knowledge of many traditional processes in which biological agents were used with little control or clear purpose. Nevertheless, it cannot be said that the modern industry of fermentative biotechnology is an updated version of the old fermentative processes used to make cheese and wine, and it cannot even be said that it is related to the microbiological discoveries of the XIX century. It is rather the result of the application of microorganisms that are selected and manipulated for specific purposes.

As an example, we shall emphasise two industrial aspects of the modern biotechnology of fermentation: in the first place, obtaining biomass from activated sludge and, in the second place, the large-scale selection and propagation of specific strains of Clostridium for the production of acetone and butanol. These two processes were initiated in Manchester almost a century ago now, and both are a paradigm of the biotechnological process in the broad sense of the word and examples of both fields of the biotechnological industry.

1.2.1. The beginnings of biotechnology

In many ways, biotechnology is an ancient science. Thus, without knowing the principles of fermentation or genetics, humanity has been implementing some biotechnological processes since ancient times, for example in the production of cheese, bread, wine, the selective breeding of animals and plants and so on.

As for the term biotechnology, it was coined by Karl Ereky in 1919 to describe the interaction between biology and technology; nevertheless, biotechnology is not just biology and technology. Rather it has been a multidisciplinary effort by mankind for over 5,000 years. When man began to grow plants or rear animals, make beer or wine or produce cheese, he was applying the principles of biotechnology in the broad sense of the word. That is to say, the first phase of biotechnological development is the use of fermentation techniques. It was not until later, in the seventies, that it began to be applied to the spectacular results of the emerging techniques of molecular biology. Finally, in more recent times, this term has been introduced into common language.

Below is a list of the most relevant milestones in ancient biotechnological processes:

- alcoholic beverages (prehistoric times),
- the making of beer (3000 BC),
- the making of bread (3000 BC),
- the making of vinegar (14^{th} century),
- Leeuwenhoek's description of yeast cells (1689),
- The discovery of the fermentation properties of yeast by Erxleben (1818).

There are numerous traditional applications of biotechnology. A simple example is compost, which increases the fertility of the soil allowing the earth's microorganisms to break down organic matter. Other frequent applications are the production and use of vaccines. There are also a multitude of examples of biotechnological processes in the food industry: the making of wine, beer, cheese, yoghurt, bread, etc.

1.2.2. Modern biotechnology

Today's current interest in biotechnology lies in the potential of the union of biological processes and methods —ancient and new— with the techniques of chemical engineering and electronics. Modern biotechnology could be graphically represented as a tree whose roots are the biological sciences (microbiology, genetics, molecular biology, biochemistry) and whose branches are the chemical engineering of processes in their broadest sense.

The birth of modern biotechnology is associated with the development, on an industrial scale, of the processes of making penicillin. During the Second World War, antibiotics were in great demand and this led to the collective effort by chemical engineers and microbiologists to obtain large-scale production of penicillin by fermentative methods.

Later, the modern biotechnological industry proposed the use of enzymes as an objective. Enzymes are the active ingredients of microorganisms and are, in reality, responsible for bioreactions. Unlike microorganisms, enzymes have the advantage of being manipulable almost like a chemical molecule, they have fewer secondary reactions and they do not multiply, and thus, problems of biomass do not arise. However, this last point, may be a disadvantage, since enzymes often need coenzymes or mediators in order to act and, once deactivated, become useless for bioreactions.

The first applications of enzymes in the biotechnology industry were the manufacture of sweeteners (for example, obtaining fructose syrup from wheat) and the example of lipases and proteases in detergents to remove difficult stains from fabrics.

With the use of specific enzymes, many obtained from genetically manipulated microorganisms, the second generation of industrial biotechnology (or modern biotechnology) began, which now clearly integrates microbiology, biochemistry and process engineering.

1.2.3. The latest generation of biotechnology

Biotechnology started to be considered as being a modern science in the seventies due to the advances in molecular and genetic biology. These advances gave rise to the techniques of cloning and recombinant DNA that provided scientists with greater knowledge of the workings of cells and their components in living beings and made it possible to develop new methods to isolate stem cells and genes of living organisms to produce products of their metabolism in vitro which had previously only been obtainable from the living organism.

Modern biotechnology has not shunned its past, on the contrary, it has integrated it into the new methods and techniques. Thus, modern biotechnology covers a broad spectrum of products and services supported by the current spectacular advances in the techniques of genetic engineering.

The ability to manipulate genetic information at its most basic level, DNA, has caused an exponential increase in the number of biotechnological companies devoted to the techniques of recombinant DNA. Many pharmaceutical products are already obtained with designer enzymes and microorganisms, specifically products that include substances such as insulin, interferon or activator plasmids, which were previously either highly complicated or expensive to manufacture.

However, an erroneous conception, as it is too restricted, is the one that circumscribes biotechnology only to recombinant DNA techniques. Let us recall once again that modern biotechnology is far more than just this; it is the application, in a multitude of fields, of manipulated or selected organisms with these techniques to obtain products with added value.

Therefore, the types of technology that may be included in the modern concept of biotechnology are:

- recombinant DNA (genetic engineering),
- vegetable tissue cultures,
- mammal cell cultures,
- biocatalysts,
- the treatment and reuse of waste products by biotechnological methods (bioremediation),
- fermentation,
- the biotechnological obtaining of fuels and organic raw materials as an alternative to oil,
- biotechnological process engineering.

In addition to the field of health, we feel it is also important to stress other current applications of biotechnology including the use of genetic engineering: bioremediation and cleaner technologies.

Traditionally, the methods for the treatment of toxic and organic waste have often been expensive and may create new environmental difficulties. Genetic manipulation has allowed us to obtain low-danger microorganisms and specific enzymes to degrade and metabolise toxic waste products. This use of manipulated or selected microorganisms, or of the enzymes they produce for the field of waste treatment is called bioremediation. Examples of bioremediation techniques are the obtaining of methane and gases from urban solid waste (USW), the digestion of vegetable waste by bacteria, biopurifiers, the obtaining of biomass from organic by-products, the breaking down of oil slicks by micro-organisms, etc.

On the other hand, in different industrial sectors, biotechnological techniques are currently being applied to substitute environmentally hazardous or pollutant industrial technologies. These new techniques use microorganisms or enzymes to achieve a cleaner, less polluting technique and waste that is more easily biodegradable. In this way, not only are the harmful effects of waste and even the amount of such waste reduced *in situ,* but also water and energy expenses.

1.3. MAIN BIOTECHNOLOGICAL AREAS

Biotechnology can be classified in two ways, one horizontal which distinguishes between the techniques used (areas of biotechnology) and the other vertical, concentrating on the sectors of industrial application.

The previously cited areas of biotechnology, which we shall now discuss in greater detail are:

• recombinant DNA (genetic engineering),
• vegetable tissue culture,
• mammal cell culture,
• biocatalysts,
• the treatment and reuse of waste products by biotechnological methods (bioremediation),
• fermentation,
• the biotechnological obtaining of fuels and organic raw materials as an alternative to oil,
• biotechnological process engineering.

1.3.1. Recombinant DNA and genetic engineering

Molecular biology has made the most important finding in biotechnology possible: today we can separate the gene which is responsible for codifying the production of certain substances and transfer it to another host organism thus achieving the more effective production of certain useful proteins. Thanks to this breakthrough, hormones, vaccines, blood coagulation factors and enzymes are biotechnologically produced today on a large scale. On the other hand, with the biotechnological production of proteins, the difficulties involved in obtaining them from superior organisms is thus avoided:

• It is not practical to cultivate cells of superior organisms on a large scale because they grow slowly and are easily contaminated. It is more practical to cultivate microorganisms.
• The cost of a cell culture is higher than that of microbial cultures.
• The source of cells of superior organisms is far more limited than the source of unicellular organisms, which, moreover, reproduce easily and quickly.

This area of biotechnology also offers the possibility of obtaining new proteins. For example, the production of enzymes as biocatalysts. In the case of biocatalysts, their specific capacity is governed by molecular structure and by means of the recombinant DNA technique, the genes that codify the cellular synthesis of enzymes may be selectively modified. Then, when transferring the new DNA to a host microorganism, a new productive strain of the desired enzyme may be obtained.

1.3.2. Plants and vegetable tissue culture

Apart from their key role in the production of food, plants are an important source of raw materials and medicines. To this end, it should be remembered that 25% of drugs today are of vegetable origin.

On the other hand, the culture of unicellular vegetable organisms to produce biomass or to extract products of high added value is a practice that is intensifying from day to day, as molecular biology prospers.

Finally, experiments have already been successfully performed on the reproduction of modified plants by means of replication techniques. At present this technology has allowed us to remedy shortcomings, improve species and increase resistance to pests and diseases in a great deal of vegetable species.

1.3.3. Mammal cell culture

The first study on the spontaneous fusion of two different somatic cells to form a heterokaryon —two or more nuclei in just one cytoplasm— was published in 1960 by Barsky and his collaborators in France. However, previously the appearance of polynuclear cells had been observed in tissue cultures of mammals infected with certain inactivated viruses (Bull [*et al.*], 1984).

Thanks to the heterokaryons it is possible to obtain the expression of the genes of both parental cells. In 1975, Kohler and Milstein applied this property in their famous synthesis of monoclonal antibodies, obtained by the fusion of lymphocytes producing antibodies with malignant myeloma cells, which can reproduce very quickly. These hybrid myeloma cells conserve the property of reproducing quickly and, at the same time express specific antibodies.

Given that some proteins are only produced from mammal cell cultures, large-scale cell culture is one of the aims of molecular biologists. Monoclonal antibodies and interferon are two examples of this type of protein, which are highly important for the preparation of therapeutic products and products of analytical application.

1.3.4. Biocatalysts

Enzymes are nature's catalysts and they show, as with all natural processes, great specificity and thermodynamic efficiency. They have been used for centuries, in particular for the production of food, and they represent one of the most ancient forms of biotechnology.

The use of enzymes —isolated or in dead or dying cells— is of great importance not just in the food industry, but also in the production of chemical substances, in systems of analysis and diagnosis, in the treatment of illnesses and, lastly, in the emerging industry of cleaner technologies.

The use of enzymes in all of these fields has been possible thanks to the greater knowledge of the way enzymes work in the metabolic systems of living beings, as well as greater knowledge of their structure and, above all, the possibility of obtaining designer enzymes by genetically manipulating micro-organisms. This has meant that many companies are devoted to the production of enzymes, of microbial origin, on a large scale.

1.3.5. Bioremediation

Let us recall that bioremediation is the application of biotechnology in the treatment and reuse of waste products. Let us see some applications in this field.

Biological treatment plants constitute a good example of simple applied biotechnology. In this case, it is a fixed bed of microorganisms that degrades organic waste products to acceptable levels in water that is to end up in a river or stream. The sludge from these treatment works is used as biomass for animal food. There also exist biotechnological processes to treat urban solid waste (USW) with aerobic or anaerobic fermentation to obtain biogas.

Another example of this technique are the assays for the treatment of specific problems using biotechnology, for example, digestion, with micro-organisms, of oil slicks at sea, following an accident in which oil is spilled.

Also in this field, studies are made on the microbial degradation of cellulose waste to obtain biomass (unicellular proteins). It has been estimated that the amount of proteins that could be obtained in this way, from agricultural waste, may be enough to feed the world population.

Lastly, other studies are currently underway: the application of biotechnology for the detoxification of polluted soil. This technique uses cultures of superior plants, which act as heavy metal fixers and eliminate organic pollutants.

1.3.6. Fermentation

Fermentative processes together with biocatalysis share being the most ancient forms of biotechnology. Fermentation is the application of the microbial metabolism in order to transform a material into products of added value. This process can produce an incredible variety of useful substances, for example: citric acid, antibiotics, biopolymers, unicellular proteins, etc. The potential is immense and highly varied. We only need to know the appropriate microorganism, control its metabolism and growth and be able to use it on a large scale.

1.3.7. Fuels and organic products as an alternative to oil

Oil is a non-renewable raw material, which means that its uncontrolled or growing use is limited. On the other hand, biotechnology uses renewable materials, which is the reason why its controlled use could be infinite. Therefore, faced with the possibility of running out of oil, biotechnology can contribute two solutions: on the one hand, new fuels and, on the other, an alternative source of organic products. For example, one process, which is economical in terms of energy, is the use of the waste products from the manufacture of sugar cane to obtain alcohol.

Another potential fuel obtained biotechnologically is methane, which comes from the fermentation of agricultural waste (biogas). This biotechnology is easily adaptable to agricultural societies with limited resources.

The most sophisticated biotechnological fuel, and perhaps the most desirable is hydrogen derived from the biophotolysis of water. This technology is based on combining the photosynthetic capacity of chlorophyll from vegetable cells and the hydrogenase activity of an enzyme of bacterial origin. The great advantage of this fuel derived from water is that it does not produce pollution when burnt and its original reactive can regenerate. Unfortunately, this technique is still only at the study stage.

1.3.8. Biotechnological process engineering

From the application of chemical engineering techniques to the biotechnological processes has arisen the science of bioreactors, a technical area that is as much linked to chemical engineering as to biology, microbiology and biochemistry which covers the study and design of fixed bed reactors, pH control and temperature probes, dosage pumps for reactives and aeration; the design of agitators; the study of the different methods for the immobilisation of enzymes and micro-organisms, and the design of different filters. All of these techniques together have come to be known as process engineering. All of this biotechnological knowledge needs to be transferred to a production scale to make it profitable, and often, this transfer requires scaling processes and technology from the field of engineering, which must be adapted to the specific properties of the living organisms with which biotechnology works. Some examples of these processes are: the collection, pre-treatment and filtering of raw materials; the design of the reactor; the recovery and reuse of biocatalysts; the extraction and analysis of products; the treatment of effluents, and the recycling of water.

1.4. INDUSTRIAL AND GEOGRAPHICAL SCOPE OF THE STUDY

Modern biotechnology is well introduced in industrial sectors, such as the pharmaceuticals industry, fine chemistry and the food sector, in developed countries of the western world, principally in the United States and Japan. In these countries, the aforementioned sectors can support the high cost involved, until today, in the research into biotechnology. This cost is due, in the case of the pharmaceuticals and fine chemistry sectors, to the high added value; and, in the agricultural and foods sector, to the large volume of products manufactured.

Currently, the large-scale production of designer enzymes, which has been made easier by the new technologies of genetic engineering, and the fact that the proliferation of companies producing microbial enzymes has made them easier to acquire has brought down the costs of applied biotechnology, and especially biocatalysis. And, together with this, the use of selected and tested microorganisms in industries devoted to fermentation has also been facilitated. In this way, the field of the bioremediation industry has opened up and it has been possible to apply biotechnological techniques to industrial sectors where it was previously unthinkable due to the low volume of their products or their low cost. In addition, growing environmental awareness and legislation, which is more and more restrictive, applied to this field in Europe and the First World have stimulated some sectors —such as textiles, the paper industry, tanning, etc.— to apply biotechnology in some of their processes in order to improve yield and move towards cleaner, environmentally more sustainable technology.

The Mediterranean area, especially in the South, has a large number of small businesses in the food, textile and tanning sectors. These sectors, together with the issues of managing Urban Solid Waste (USW), offer a vast field of opportunities for biotechnology. In the most developed countries of the Mediterranean, biotechnology is already applied in such sectors as food, pharmaceuticals, fine chemistry, textiles and paper and also in bioremediation and waste treatment. However, in countries of the Southern and Eastern Mediterranean, with the exception of Israel, this technology is less widespread but is beginning to be introduced, especially in the fields of bioremediation and waste treatment.

2. APPLICATIONS IN THE INDUSTRIAL SECTOR

Companies use industrial biotechnology to:

- reduce costs,
- increase earnings,
- raise the quality of their products,
- optimise the process and its follow-up,
- improve the safety and hygiene of technology,
- comply with environmental legislation.

On the other hand, the adoption of strategies to prevent pollution at source allows these aims to be achieved. That is to say, by implementing other alternatives for the minimisation of pollution, among other benefits there will be a reduction in costs —both associated with the management of resources and the management of waste flows, an increase in the quality of the products, a decrease in non-compliant products and the optimisation of the consumption of resources —by means of the revision of the control parameters of industrial processes. And, of course, this will lead to an improvement in the conditions of safety and hygiene and in compliance with environmental legislation.

Thus, biotechnology is considered one of the options that may be included either as an alternative to the implementation of new technologies and as a substitute for potentially polluting raw materials or in the application of good housekeeping practices, integrated within product redesign, favouring the reduction at source of waste flows associated with the production process.

The laws and regulations in the modern United States continuously impose controls on the industrial use of chemical products. Industry, is showing a growing interest in the direction of sustainable development, which is positive. Our future economic health depends on the reduction of industrial pollution and saving natural resources, which is the reason why both public and private bodies are promoting the tendency towards green alternatives in the industry of products and services.

In order to achieve cleaner production and a reduction in waste, we must take two key factors into account, both in industry and in society: clear, realistic legislation which defines the maximum permissible levels of pollutants, as well as a clear policy of aid for industry and research centres to apply and develop projects in the field of the environment.

Next, we shall proceed to study in greater depth some applications of the biotechnological areas which are most applied in bioremediation and the cleanest technologies: enzymatic biocatalysis and microbial fermentation.

2.1. BIOCATALYSIS: THE APPLICATION OF ENZYMES IN THE INDUSTRIAL SECTOR

Enzymes are increasingly important in sustainable industrial growth. Enzymes have already been used in the development of industrial processes to obtain waste-free products or products that have a minimum of biodegradable waste. Given that in the not-too-distant future manufacturing companies will have to pay great attention to make all waste compatible and also in the recycling of used water, enzymes may solve many of these problems. In fact, in some processes, enzymes can substitute toxic or corrosive chemical products. Moreover, they have the advantage of being used, deactivated and then they decompose in simpler totally biodegradable products.

Many industrial processes operate at high temperature or pressure, or in highly acid or base conditions. Enzymes can avoid such extreme conditions and corrosive reactives. Enzymes work at moderate temperatures, at atmospheric pressure and in solutions which are close to neutral pH. They are highly specific catalysts which yield purer products with fewer secondary reactions. Therefore, all processes that substitute chemical substances with enzymes will pollute less, will respect the environment more and will be cheaper.

Below we offer an overview of the enzymatic processes that are already currently used in many sectors to reduce the chemical load eliminating, from industrial production, aggressive and toxic substances or simply pollutants (Sayler, 1997).

- **Detergent industry:**
  - enzymatic degradation of proteins, starch and fat stains for the washing of clothes;
  - the use of lipolytic enzymes in dishwasher substances;
  - the use of enzymes as surfactants.
- **Textiles industry:**
  - stone washing for denim fabrics,
  - enzymatic desizing of flat-woven cotton fabric,
  - ecological bleaching,
  - enzymatic scouring of cotton fabrics,
  - enzymatic desizing of silk.
- **Starch industry:** the enzymatic production of dextrose, fructose and special syrups for pastry, preserves and the soft drinks industry.
- **Brewing industry:** the enzymatic degradation of starch, proteins and glucans which come from mixing cereals used in making beer.
- **Pastry and baking products industry:** the enzymatic modification of carbohydrates and proteins in cereals to improve the properties of bread.
- **Wine and juice industries:** the enzymatic degradation of fruit pectin, in the making of juices and wine.
- **Alcohol industry:** the degradation of the starch in sugars for their later subjection to fermentation thus obtaining alcohol.
- **Food and additives industry:**
  - improvement to the nutritional and functional properties of animal and vegetable proteins,
  - conversion of the lactose in milk and the whey into sweeter, more easily digestible sugars,
  - production of cheese aromas.
- **Animal feed industry:** the enzymatic hydrolysis of proteic matter coming from slaughterhouses to obtain flour with high nutritional value for animal feed.

- **Cosmetics industry:** biotechnological production of collagen and other products for their application in beauty creams.
- **Paper industry:**
  - the enzymatic dissolution of pitches,
  - the ecological bleaching of paper pulp,
  - the enzymatic control of the viscosity of starch stucco.
- **Tanning industry:** the preparation of hide and the elimination of hair and fat.
- **Oil and grease industries:** the enzymatic hydrolysis of fats and lecithin and the synthesis of esters.
- **Fine chemistry industry:** the synthesis of organic substances.

2.2. THE MARKET FOR ENZYMES

Today it is estimated that the world market for enzymes is worth approximately 1,108 million euros. The market is divided, according to the industrial application industrial of enzymes, as follows:

Detergents	45%
Textiles	14%
Starches	13%
Pastry, wines and juices, alcohol and food	18%
Animal feed, paper, leather, fine chemistry and fats and oils	10%

The most frequently used enzymes are proteases, amylases and cellulases. Despite the enzymes being broadly used in industry, they only represent a small amount of the total market of chemical products. This is due to the following reasons:

- The lack of sufficient enzymological knowledge in many industrial sectors.
- The resistance to incorporate enzymes into old manufacturing processes due to the investment required in new equipment and materials.
- The hurdle represented by the change of attitudes in some sectors.
- Given that finding the right enzymes for each process is of great importance, prior enzymatic screening is required.

2.3. ENZYMES FOR SUSTAINABLE DEVELOPMENT

Now we shall comment on some enzymatic processes that are used in industry to provide more environmentally friendly technical solutions.

2.3.1. Starch processes

In regard to starch-related processes, amylases have been used for the last 50 years to substitute the acids in the hydrolysis of starch to obtain its liquefaction. In the seventies, alkalis were replaced by isomerases, in obtaining fructose from glucose.

Traditionally, the process for obtaining dextrose from starch was carried out in an acid medium (pH=2) and at 140 ºC. Obtaining thermostable bacterial alpha-amylases meant that dextrose could be obtained without acid hydrolysis and at a lower temperature.

Today, a variety of enzymes are used to obtain several products from starch: bacterial and fungal amyloglucosidase, debranching enzymes such as pullulanase, etc. The end result of this process is more efficient, consuming less energy and producing less toxic waste.

2.3.2. Detergents

The detergents industry, as we have seen previously, is the industry that uses the most enzymes, 45% of the market total. The enzymes used in this sector are protease, bacterial and fungal, amylases, cellulases and lipases.

The most common on the market are the bacterial proteases, a great variety of which exist today. They have growing cleaning properties and a great stability to oxidants.

Alpha-amylases are highly efficient for the degradation of starch chains and that is why they improve the elimination of dust and soil particles that become trapped in the fabric in the weft of starch polymers.

By using proteases and amylases together, better fabric washing is achieved, the chemical product load in the detergent is decreased and the wash temperature can be reduced.

As for the cellulases, they are used in place of ionic surfactants in order to improve the softness of cotton fabric. Furthermore, they are also active in eliminating the dust and soil particles since they eliminate the microfibres from the cotton fibres, which additionally produces a brightening effect on the colours.

Lipases, on the other hand, catalyse the hydrolysis of the triglycerides present in fat stains, making them hydrophilic and easily eliminated during washing.

Finally, we must point out that the enzymes used in detergents have a positive impact on the environment. Indeed, they imply an energy saving due to the reduction of wash temperatures, they enable the chemical content of detergents to be reduced, they are biodegradable, they have no negative impact on water purification processes and they do not present a risk for aquatic flora and fauna.

2.3.3. Dishwasher detergents

Traditionally, dishwasher detergents have contained high concentrations of phosphates and silicates, giving the water high alkalinity. Moreover, chlorate derivatives coming from bleach are found in their composition.

Concern for the environment has led the manufacturers of these products to use enzymes in dishwasher detergents. In this way, the use of proteases, lipases and amylases has meant a decrease in the consumption of chemical products, at the same time as more efficient, safer detergents have been obtained.

2.3.4. Surfactants

Surfactants are substances whose molecular structure contains hydrophilic groups and hydrophobic groups. They manage to achieve stable emulsions, which are used, for example, in powdered detergents, shampoos and cosmetic creams. In food, these substances are used as emulsifiers.

The structure of surfactants means that they can adhere to the two surfaces in the interface and, in this way, can reduce the surface tension by producing stable microemulsions. This process allows solid products to become soluble and disperse rapidly. Surfactants also alter the foaming properties of heterogeneous solutions, producing stable foams, and, therefore, they are used in the food industry, for example in the case of creams.

Until recently, all surfactants were synthetic, deriving from oil and required reactive agents such as pyridine, dimethyl sulfoxide, etc. Current enzymology has made it possible to create another type of natural surfactant, such as the glycolipids, using commercial lipases to obtain them. Specifically, glycolipids are fatty acid esters and they behave better than synthetic surfactants, as emulsifiers of fats and oils. Moreover, they degrade forming natural sugar molecules and non-toxic fatty acids. It has been proved that their use is totally environmentally friendly, since the process does not include the use of organic solvents or chemical substances for synthesis.

2.3.5. Textiles desizing

Starch is the natural substance which is used to cover cotton yarn prior to weaving in order to increase its resistance. This starch must be eliminated before proceeding with the final fabric treatments: bleaching, dyeing, special treatments, etc. Traditionally, this elimination was done in acid medium. Now, amylases are used in the enzymatic desizing, eliminating the acid from the process. The textiles industry has used this biotechnological process since the beginning of the 20th century. The amylases work most efficiently in the process of desizing, without the problem of environmentally hazardous waste such as mineral acids, bases or oxidising agents.

2.3.6. Leather

The tanning of leather is one of the oldest industrial processes to use enzymes. The stages of the traditional process are: curing, soaking, hair and wool removal, reduction and tanning.

The process uses numerous chemical products for the elimination of the undesired hair, fat and proteins (elastin, keratin, albumin and globulin), leaving the collagen intact at the stage prior to tanning. The chemical products used at these stages seriously harm the environment. This is why, today, in the process of tanning, proteases such as trypsin and lipases are used as they reduce the use of sulphites, organic solvents and synthetic surfactants, achieving a product with enhanced end properties.

2.3.7. Paper industry

In the case of the paper industry we concentrate on two processes: bleaching and dye removal.

Bleaching is the elimination of lignin from chemical paper pulps. This stage in the manufacture of paper is required for two aesthetic reasons and to improve the qualities of the end product. The bleaching process includes different stages and varies according to the type of substances used.

In the bleaching of Kraft pulp, chlorate compounds have traditionally been used. This method produces toxic —mutagenic, carcinogenic, bioaccumulable— waste, which cause numerous alterations to biological systems. This is why the use of these bleaching agents is starting to be forbidden in different developed States.

An alternative to chlorinated bleaching agents is the use of enzymes. Thus, the use of xylanases in the process of bleaching Kraft pulp eliminates the use of chlorine and reduces toxic waste. Furthermore, it removes the bottleneck from the process (due to the limited capacity of the chlorine dioxide tanks); it increases the degree of whiteness of the pulp and reduces the process costs, principally at factories that use large amounts of chlorine dioxide. Lastly, pre-treatment using enzymes also increases the degree of final whiteness of the pulp and reduces the chemical agents used in the bleaching stage.

A process of deinking is required if recovered fibres are to be used as a raw material in the manufacture of paper and cardboard, since for their later use, dye and other pollutants pertaining to this raw material must be removed. However, deinking presents setbacks when using recycled paper and, furthermore, it produces new solid and liquid waste.

In the deinking processes, the following enzymes are used: lipases, esterases, pectinases, hemicellulases, cellulases and ligninic enzymes. The first two, lipases and esterases, degrade the dyes which are based on vegetable oils. The remainder —pectinases, hemicellulases, cellulases and ligninic enzymes— modify the surface of the cellulose fibre or the unions close to the dye particles, in such a way that the dye is freed from the fibre and can be separated from it through flotation or washing.

2.3.8. Baked Products

Research into the reasons why bread goes stale or hardens has a long history and no answers. Many bakers use chemical emulsifiers, such as monoglycerides, to postpone the hardening of the bread. Nevertheless, since some years ago, enzymes, which are more natural substances, have been used to retard the hardening process in bread. Specifically, amylase increases the sensation of the freshness of bread compared with chemical agents.

2.3.9. Biocatalysis

The importance of enzymes in the synthesis of chemical products is becoming more and more recognised. Some examples, which are now current, of products obtained by means of enzymatic catalysis are aminoacids, pure quiral molecules and antibiotics such as penicillin and ampicillin.

The synthesis of products with biocatalysts generally involves low consumption of chemical products, the reduction of non-biodegradable waste products, the specificity of the reaction, a reduction in the amount of by-products and a reduction in energy consumption. Likewise, biocatalysis offers significant advantages compared to conventional chemical processes: it means that moderate pH, temperatures and pressure can be used and, furthermore, the by-products are reduced (Sayler, 1997).

2.4. BIOREMEDIATION

Bioremediation may be used by any company, and is normally used to transform waste and purify water or the soil. This process mainly uses microorganisms. Let us see how these microorganisms act in some of the most commonly implemented bioremediation today:

- Biological treatment plants: a colony of microorganisms decomposes the organic matter in the wastewater.
- Bioremediation of polluted soil: the colony of microorganisms is sown on a plot of land with specific pollution and the colony of microorganisms metabolises the pollutants.
- The digestion of oil slicks: the microorganisms metabolise the carbohydrates spilled from the oil.

2.5. THE PRODUCTION OF BIOGAS AND ALCOHOL

The production of biogas and alcohol may be used to reduce or transform waste which is rich in organic matter. Much waste may be useful: the sludge from biological water treatment plants is a good substrate for obtaining methane by anaerobic fermentation; the waste generated by sugar plants, rich in carbohydrates, is used as substrate for fermentation to obtain biogas (anaerobic fermentation) or to obtain alcohol (aerobic fermentation), and urban solid waste is used as a substrate for anaerobic fermentation to obtain biogas.

3. CASE STUDIES

Of the case studies described in this chapter, the first six have not been taken from the Mediterranean area; however, some of the techniques used have also been implemented in the European countries of the Mediterranean.

3.1. CASE STUDY 1: BIOREMEDIATION

Lattice Property (Basingstoke, United Kingdom)

Bioremediation offers a cheaper option for the decontamination of soils and, in the long term, a more sustainable option, since it uses the natural ability of microorganisms to metabolise a broad spectrum of organic pollutants, from oil hydrocarbons to PCB-type polychloride pesticides, and heavy metals such as lead.

The case shown here is that of Lattice Property, a company that has several gas production centres, in some of which the soil was polluted. It has currently completed up to 150 research and remediation projects of all those which have been started.

The project described here was applied at an abandoned gas production centre in Sheffield. Having carried out digging, four tanks were found containing tar and polluted water. This material could have been destroyed or sent to special landfills, at a cost of 63 to 94 euros/m^3. However, the company decided to sow the polluted land in order to speed up the microbial decomposition of the tar. This option only requires the addition of water and nutrients to the tar, with no further organic additives, and is controlled thanks to a cycle of covered, monitored cultures. The chosen process has a low cost, but is a long one. Nevertheless, given that the company was not in a hurry, this process was considered suitable.

Benefits	Setbacks
• A saving of almost 47 euros/m^3 compared to the cost of landfill handling charges. • Adaptable to any size of polluted soil. • Low investment in infrastructures. • Effective environmental management to improve sustainability. • Not necessary to transport the polluted soil.	• A long process.

3.2. CASE STUDY 2: CLEANING

Expert Heat Treatments (Stillington, United Kingdom)

Expert Heat Treatments (EHT) is a company located in Stillington, which treats surfaces. In 1999 it had to review its pre-treatment line because the parts to be treated (car valves) were covered with a fine layer of oil that had to be removed before the thermal pre-treatment for it to be effective.

Traditionally, EHT used an organic solvent in a steam degreasing tank for this cleaning process. However, for several reasons (the increased cost of the solvent, more restrictive legislation concerning the use of organic solvents, greater environmental awareness, etc.), the company considered alternative cleaning methods. Tests were made using a cleaning enzyme formulated to degrade mineral oils and grease. Since these tests performed in the laboratory, prior to the thermal process, gave good results, the process was scaled up in order to ascertain its effectiveness on an industrial scale, and it was concluded that the degreasing effectiveness was comparable to that of the system implementing the solvent. Finally, it was decided to incorporate this method of degreasing on the new line of pre-treatment in January 2000.

Benefits	Setbacks
• The company has saved 10,163 euros. • The functioning cost of the new line is 74% cheaper. • The enzyme is biodegradable and can be safely poured into the drainage system. • There are no toxic emissions into the air and the whole process is safer, since no product is a pollutant.	• (None)

3.3. CASE STUDY 3: VOC REDUCTION

BIP (Warley, United Kingdom)

BIP Ltd. manufactures a wide range of products for the textiles and paper industries. The company, faced with increasing pressure concerning the regulations for the reduction of VOC emissions (volatile organic compounds), decided to work towards the reduction of volatile matter.

Indeed, the production of powdered melamine gives off a large quantity of VOCs, which contain formaldehyde and methanol. When studying the process, it was concluded that the stage producing the highest emissions was the melamine drying process. The target was to reduce VOC emissions from 200 mg/m^3 of air to 5 mg/m^3 for formaldehyde and to 80 mg/m^3 of air for methanol. The biotechnological solution was chosen because it was cheaper than other conventional solutions (scrubber, incinerator).

In this case, the biotechnological solution consists of the installation of a bioreactor in which a colony of microorganisms degrades the formaldehyde and the methanol down to carbon dioxide and water. The air, loaded with the pollutant VOCs, passes through a humidifier and a particle filter. Then, it enters the bioreactor containing the microorganisms. This bioreactor produces a small amount of water, which goes to the treatment plant, although it could also be channelled into the sewerage system.

This system, which was set up in 1997, uses specifically selected natural microorganisms for the metabolism of methanol and formaldehyde and incorporates an automatic system for the regulation of the temperature, pH and the biomass level. As far as its installation is concerned, given that it is relatively small, it can be installed on the roof of the process plant.

Benefits	Setbacks
• A saving of 156,349 euros per year, comparing this technology with incineration. • Safe process in compliance with legislation on VOC emissions. • Minimal maintenance. • Environmentally friendly.	• The small investment in the bioreactor.

3.4. CASE STUDY 4: CLEANING

Dundee Electroplating (Dundee, United Kingdom)

Dundee Electroplating Ltd. deals with zinc galvanising. To begin galvanising, there must be neither grease nor dirt on the metal parts. Traditionally, the parts were submerged in a highly alkaline cleaning product and the particles were eliminated electrolytically. After 12 weeks, the cleaning solution was saturated and had to be changed. To do so, the water was discharged into the sewage system having been neutralised and the zinc precipitated in the galvanisation fluid.

In 1999, a suggestion was made to use a biotechnological cleaning system in place of the alkaline solution. This system contained a surfactant to emulsify the grease and dirt and some microorganisms to metabolise the oils into carbon dioxide and water. Some changes were made in the wash tank: the temperature was reduced from 70 °C to 45 °C (optimal temperature for the micro-organisms), an aeration system was installed to supply oxygen to the micro-organisms and to obtain the agitation of the submerged parts and two biological cleaning tanks were installed that are continuously operative, with no need to change the solution every two weeks. After a few days, equal or greater cleaning efficacy to the previous system had been achieved in a similar length of time. However, this new system needed more monitoring and maintenance than the previous system.

Benefits	Setbacks
• Saving in the cost of purchasing chemical products. • Saving time and work changing the cleaning solutions. • Compact equipment. • Low environmental risk, smell-free system. • Reduction in the consumption of energy in the electrocleaning tank and conservation of the efficacy of the electrode.	• Requires more monitoring of tanks. • Equipment maintenance.

3.5. CASE STUDY 5: WASTEWATER

British Sugar (Peterborough, United Kingdom)

British Sugar Plc. has seven plants in the United Kingdom and produces 1.3 million tonnes of white sugar per year using beet as its raw material.

The manufacturing process begins with the transport of the beet to the plant, where it is washed and separated from the earth, stones and grass. The water flows towards a clarifier and the sludge remains at the bottom. This sludge ends up in the sedimentation tank. The clarified water returns to the circuit to be reused. This water and sludge must be treated before being discharged in order to reduce the COD.

The traditional treatment of wastewater consisted of an aeration system and discharge into the sewage network, but this system had insufficient capacity to treat all of the water. An alternative biological system was studied for the treatment of all waste products so as to be able to directly discharge into the river, but there were also problems of the smell and acidity of the sludge. So, it was decided to set up an anaerobic digester. The system consists of passing the wastewater over a bed of biomass granules. A three-phase separator in the upper part of the digester separates the biomass from the gas and the treated water. The biogas can be used as a fuel, the biomass returns to the digester and part of the treated water re-circulates in the digester to maintain a constant flow of treatment water. This digester came into operation at the end of 1996 and eliminates 12 tonnes of COD per day at 80% efficiency.

Benefits	Setbacks
• The effluents can be directly discharged into the river. • A saving of 1,250,840 euros/year in the treatment of effluents. • A saving of 114,143 euros/year in fuel (as the biogas is harnessed). • Low maintenance and compact equipment. • Odourless system.	• (None)

3.6. CASE STUDY 6: BIOPULPING

In the paper industry, pulping operations are divided into two kinds: mechanical processes and chemical processes, which lead to the fibre acquiring different characteristics. Very often, however, a combination of the two processes is implemented in order to obtain a paper with specific characteristics.

The mechanical pulping of wood represents 25% of the pulping process worldwide, but this figure is expected to increase in the future. Nevertheless, this system uses a great deal of electrical energy, and this limits the use of mechanical pulping in many types of paper. Biopulping is a technology that reduces the costs of electrical energy and the environmental impact of the pulping process, thus increasing the system's economic competitiveness.

Biopulping is a process that saves energy and improves the resistance of the paper. Nonetheless, difficulties exist in the scaling of the process. For twelve years, in the United States, a consortium made up of the USDA, the Forest Service, the Madison Forest Products Laboratory and Wisconsin and Minnesota Universities have made a special effort to research this field. The project was sponsored by 23 companies related to the paper industry, the Energy Center of Wisconsin and New York State University. The project got underway in April 1987.

Biopulping consists of using fungi that degrade lignin. A great many biological variables have been optimised such as the species of fungi, the form of the inoculum, the size of the inoculum, the type of wood, the pre-treatment of the chips, the incubation period, aeration, the nutrients, etc. Each variable was examined independently, and following the collection of data, it could be established that there were three primordial variables:

- The suitable selection of the strain of fungi: the fungus *Ceriporiopsis subvermispora* was chosen, which degrades lignin, both for leafy trees and conifers.
- The decontamination of the chips with preheated steam.
- The quantity of inoculum: this was reduced from 3 kg/t of wood to 5 g/t of wood adding a source of nutrients to the inoculum suspension, which provides the starting point for the growth of the fungus and reduces the amount of inoculum necessary.

Benefits	**Setbacks**
• Biomechanical pulp brings down electrical energy costs by 30%. • The improvement of some of the paper's resistance properties. • A reduction in environmental impact.	• The preparation of the inoculum.

3.7. CASE STUDY 7: TRANSGENIC VEGETABLES

EGYPT

The Process

In 1992, a cooperative research agreement was reached between AGERI (Agricultural Genetic Engineering Research Institute in Egypt) and the MSU (Michigan State University) to carry out the ABSP (Agricultural Biotechnology for Sustainability Productivity project). Its ultimate goal was the production of a variety of elite Egyptian crops-namely potatoes, maize, cucurbits, and tomatoes resistant to major pests to render Egypt's agrosystem more economically successful as well as environmentally safe.

At an inaugural implementation workshop held in Cairo, the partners developed work plans to focus tasks for the first year of collaboration. Teams of scientists from both Egypt and the United States were established to address specific commodity constraints and, even more importantly, the policy to be followed in the control of product biosafety and intellectual property rights and the management of networks within the project.

The potato team comprised scientists from both groups. It should be mentioned that Michigan State has an established potato breeding and genetics program with a great deal of experience in field testing transgenic potatoes.

The team concentrated on specific goals: to use transgenic potato plants expressing toxin genes from *Bacillus thuringiensis* —(known as Bt)— as parental material in a breeding program to develop improved populations of potatoes resistant to the moth. The populations would subsequently be used to select other lines of research. Additionally, important Egyptian potato cultivars would be improved and laboratory, greenhouse, and field tests of these transgenic plants would be conducted to determine their resistance to the moth and other lepidopeteran insects.

The team identified a gene owned by Garst Seed Company (formerly ICI Seeds) —a codon-modified CryV-Bt gene— as one suitable for use in transformation. A material transfer agreement was signed with Garst allowing MSU to use the gene for research purposes within the ABSP project and to share it with collaborators in Egypt and Indonesia.

The result

In 1996, the team began to obtain results from vector construct manipulation and, as the gene was working well, began transformation of the Egyptian potato variety Spunta. By 1997, the MSU lab was able to send its first- and second-generation material to Egypt for a small field test. Now that the results of this small test have proven it successful, additional materials have been shipped to Egypt for expanded field trails at AGERI and Centro Internacional de la Patata, or CIP – the international potato centre regional office in Egypt.

Egyptian scientists were working on genetic transformations using their own Bt gene at the same time research was proceeding at MSU. AGERI's research projects have now reached the stage of evaluating genetically modified organisms and approval has been received from the Egyptian National Biosafety Committee (NBC) for various small-scale field trials, including trials of transgenic potatoes transformed with CryIA© and CryV var. *Kurstaki* delta-endotoxin genes to confer resistance to the potato tuber moth.

3.8. CASE STUDY 8: TISSUE CULTURE FOR PRODUCTION OF SECONDARY METABOLITES

SLOVENIA

Problem

Plants synthesise a lot of natural substances known as secondary metabolites. Many of these are used in pharmacy, agronomy, food industry and cosmetics. Plant growth is dependent on the climate, the economy and even the political stability of the producing countries.

Possible solution (final product, process or service)

Growing plants in vitro under controlled conditions, without pesticides and any impact on the environment and biodiversity, is the alternative way of producing economically important secondary substances. We propose to investigate the possibility of in vitro production of two pharmaceutically important substances, taxol and saponins, and of natural insecticides the pyrethrins.

Taxol

Taxol (paclitaxel), a complex diterpene amide originally isolated from the bark of the Pacific Yew tree *(Taxus brevifolia),* is an inhibitor of cell division. Clinical experiments have shown its effective activity against progressive ovarian cancer and metastatic breast cancer. It has been found to exhibit antitumour activity in patients with pulmonary, head, neck and myelogenous leukemia. Approval for clinical use of taxol was granted by the U.S. Food and Drug Administration, in 1992 for treatment of advanced ovarian and advanced breast cancers.

Before 1994 the only permitted source of taxol was the bark of *Taxus brevifolia,* which has become scarce due to its very slow growth only in rare locations in Northern America. 5,000 to 6,000 kg of bark is needed to produce 1 kg of taxol. Taxol was chemically synthesised 1994, but at least 28 chemical steps are needed, so it is not expected that commercial synthesis will be viable. More promising ways of production are to use cell culture or semisynthesis from precursors.

Saponins

The roots of *Primula veris* contain triterpenoid saponins which represent 5-10% dry weight of a mixture of saponins. The main saponin is Primula acid A, also known as Primula acid I or *primula saponin* I. Saponins are efficient substances against bronchitis and chronic cough.

The plants must be two years old before the roots can be collected, so the tissue culture would be a good alternative for the production of saponins.

Pyrethrins

Tanacetum cinerariifolium accumulates a lot of natural insecticides, the pyrethrins, in its flowers. Pyrethrins are currently the most economically important insecticides of plant origin. They are mixture of six esters of chrysanthemic and pyrethric acid. Pyrethrins are very effective against a broad range of insects with little development of resistant strains and have a 'knock-down and kill' effect on insects. One of the major advantages of pyrethrins over all other insecticides is their low toxicity towards mammals and other warm-blooded animals. They are used in agriculture, horticulture and veterinary practice.

Classically they are extracted from flowers of *Tanacetum cinerariifolium.* However, worldwide demand exceeds supply, so production in tissue culture would be an additional source of these insecticides.

The innovation

The innovation in the proposed project is to establish various types of tissue culture (callus, cell, hairy root) of plants producing the commercially important substances taxol and the saponins and the environmentally more friendly insecticides pyrethrins. Different inducers will be used to stimulate the production of substances in cultures.

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3.9. CASE STUDY 9: DESIGN OF REGIONAL SPECIFIC STARTER FOR WINE FERMENTATION

SLOVENIA

Problem

The conversion of grape must to wine is a complex biochemical process involving the extracellular and intracellular activities of several yeast strains. Spontaneous fermentation of grape juice into wine can be regarded as a heterogeneous microbiological process involving the sequential development of various yeasts and other microbial species affected by the prevailing fermentation condition in a particular tank. The outcome of spontaneous fermentation depends not only on the numbers and diversity of yeast present in must, but also upon the type of grape and its chemistry. The combined effects make the outcome difficult to predict. The lack of predictability is the weakest part when comparing spontaneous fermentation with inoculated ones. On the other hand, it is believed, based on practical experience, that indigenous yeast strains associated with specific vineyards contribute to the distinctive style and quality of wine.

The primary role of wine yeast is to catalyse the rapid, complete and efficient conversion of grape sugars to ethanol, carbon dioxide and other minor but important metabolites, such as acetaldehyde, ethylacetate and higher alcohols. The apiculate yeasts such as *Kloeckera* and *Hanseniaspora* and other genera such as *Candida* and *Pichia* produce minority components in larger amounts and are beneficial in an appropriate amount, to give each wine the adequate bouquet.

The non-Saccharomyces species carry out the first period of the spontaneous fermentations. As the fermentation progresses, the non-Saccharomyces species successively die off, leaving *S. cerevisiae* to dominate and complete the fermentation. Despite the fact that there is a succession of yeast genera and species involved in the spontaneous fermentation, only a few *Saccharomy cescerevisiae* strains control the fermentation. This fact is a result of a natural selection during the spontaneous fermentation, in which the *S. cerevisiae* strains substitute the others during fermentation according to optimal fitness in a changing environment.

The innovation

Contribution of diverse yeast species confers a complexity upon wine not seen in inoculated and guided fermentations with single strain or single species. Therefore the design of regional specific inoculum by mixed populations of *non-Saccharomyces* and *Saccharomyces* yeast seemed to be beneficial. The fermentation of grape must to wine by mixed populations of yeast may yield wines with distinct sensorial quality, fuller body and rounded structure.

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3.10. CASE STUDY 10: DEVELOPMENT AND IMPLEMENTATION OF INNOVATIVE METHODS FOR FOOD AND AGROPRODUCTS CONTAMINATION ASSESSMENT

ITALY

Problem

One of the most urgent problems to be faced at a global level is the contamination of soil and waters due to domestic and industrial activities as a wide range of toxic compounds (such as chlorinated solvents, PCBs, heavy metals and other stable chemicals) affects the quality of environmental bodies and can enter the food chain in different ways, posing serious risks for human health. Moreover, the heavy and sometimes uncontrolled use of pesticides and herbicides in agricultural practice can induce diet-mediated illness due to the contamination of foods and agroproducts. Although some of the reported increase in contamination is due to better detection and recording, it is undoubtedly a real problem.

Furthermore, the food and agroproducts market has a global perspective and, accordingly, tighter norms for food quality assurance require wide and detailed knowledge and prompt information about the quality of products. The contribution of quality food controls will then lead to significant health care and socio-economic benefits, both at the level of the individual citizen and of defined population groups.

In recent years, several techniques and methods have been developed for the quality control of food products and many of them have proved to be very promising to maximize their quality and safety. Nevertheless, there is still lack of commonly accepted detection and monitoring methods/techniques, and of validated rapid monitoring systems as well as it is remarkable the necessity of lab. networks in order to exchange information/data at regional level. The introduction and implementation of new rapid control systems for food and agroproducts, (together with proper planning and management of food production, storage and distribution) will then provide a substantial input to the reduction of risks related to contaminated food assumption.

Possible solution (final product, process or service to be achieved)

Several proposals exist for the solution of polluted food and agricultural products, for example:

- Establishment of a regional laboratory network for the exchange of information/data/methods etc. on food/agroproducts contamination assessment;
- Development of novel rapid detection/monitoring systems;
- Validation of methodologies/systems through the network;
- Creation of a common regional data base on food/agroproducts quality.

The innovation

The aim is to assure the safety and integrity of the food supply by anticipating risks, tracing the sources of contaminant chain and optimizing methods for detecting undesirable components.

The establishment of a regional laboratory network for the development and use of novel rapid detection systems, based on available emerging sensoring technologies (based both on chemical and biochemical principles), will lead to the acknowledgement and validation of the systems at regional level and will create the basis for common detection/monitoring practices.

Project promotion and formulation is a key area at ICS: after assessment for economic, environmental and technological viability, projects are put forward for funding to donors such as the European Community.

ICS has long experience in training in technology management. In this respect, several courses are organized each year, in aspects such as technology management itself, technology foresight, and business alliances.

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3.11. CASE STUDY 11: WHEAT QUALITY

ITALY

Problem

Wheat quality is a competitive factor for the production chain of all the related products (bread, pastry products and pasta): methodologies and techniques need to be developed in order to improve quality control amongst wheat growers.

Possible solution (final product, process or service to be achieved)

Molecular linkage maps of many plant species have been obtained recently and utilised in quantitative trait analysis, gene tagging, genome organisation and evolutionary study.

The innovation

New molecular probes based on DNA grids will be developed.

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3.12. CASE STUDY 12: BIOACTIVE COMPOUND FROM FRUIT, VEGETABLE AND AGROFOOD WASTE MATERIAL: IN VITRO PRODUCTION OF BIOACTIVE COMPOUNDS (FLAVONOID, ANTHOCYANINS)

ITALY

Problem

Many vegetables produce bioactive molecules as flavonoids and anthocyanins with antioxidant properties. Due to the seasonal cycle of vegetable production it is not possible to extract these molecules from vegetables at the industrial level. An in vitro method could be suitable for the pharmaceutical industry.

Possible solution (final product, process or service to be achieved)

Biotechnology allows developing in vitro production of bioactive molecules from vegetable cells.

The innovation

The in vitro production of natural antioxidant molecules could allow health care research to develop new drugs with few side effects.

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3.13. CASE STUDY 13: WHEY RECOVERY

ITALY

Problem

Whey at the moment represents a waste problem for the dairy industry. It needs to find innovative solutions to convert the whey from company cost into a source of profits.

Possible solution (final product, process or service to be achieved)

The high concentration of proteins and lipids in the whey could be suitable for the extraction and purification of these molecules in order to use them in special food for diet and health care.

The innovation

New purification techniques will be developed through molecular imprinting technology.

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4. EXISTING RESOURCES IN THE MEDITERRANEAN REGION

4.1. INTRODUCTION

This study aims to describe the current situation[15] regarding biotechnological development in the countries which are signatories to the Mediterranean Action Plan (MAP).

First of all, it should be pointed out that there are significant differences in the levels of understanding, knowledge and awareness of biotechnology in the different Mediterranean countries. The role of the media and consumer organisations also vary from country to country, as well as the type and depth of the public debate on the risks and ethical issues associated with biotechnology involving major stakeholders such as government, R&D organisations, industrial associations, NGOs and others.

Secondly, it should be noted that most of the information has been obtained from the information made available to the public by the respective government bodies of these countries. We have tried to present the most accurate information on scientific and technical centres where applied research is carried out. In many cases, where explicit data on biotechnology is scarce or non-existent, we have had to interpret and identify biotechnological development as part of R&D programmes, which by their very nature, aim to stimulate competitive development of countries through science and technology.

Furthermore, globalisation creates change in the political, economic and technological arenas, which themselves are closely related. Industry in some Mediterranean countries (especially those which at a future date will become members of the European Union, such as Turkey), needs to break into unfamiliar markets, this is why these countries need to improve both their products and their production technology. For this reason, they need to assimilate new rules and regulations based on those laid down by the European Union.

4.2. BIOTECHNOLOGY IN SPAIN[16]

Spain has extraordinary potential for the development of biotechnology based on a national system of innovation, which is structured according to bioregions and “bioclusters” with a great capacity to generate knowledge and transfer technology to companies and society. The sector’s turnover has been consolidated in recent years at some 2,700 million euros.

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[15] The current state of biotechnological development in the MAP countries and of biotechnological companies and the industrial climate of each country in the region can change significantly. For this reason, information related to the companies and institutions mentioned in this document could be incorrect or obsolete. No company or institution is responsible for the information contained in this document. The authors recommend direct contact with these bodies via the addresses noted to obtain information relevant to your respective interests.

[16] According to observations of the Spanish focal point, this section refers little to genetically modified organisms (GMO), that are part of the most modern biotechnology.

Biotechnological information in Spain is not lacking, but neither is it plentiful. However, Spain's joining the European Community has greatly contributed to the updating of information in the biotechnological sector and moreover, the promotion of the creation of companies in this field has allowed the setting up of the Spanish Association of Biocompanies (Asociación Española de Bioempresas - ASEBIO). On the other hand, in a more academic sphere, the Spanish Biotechnology Society (Sociedad Española de Biotecnología - SEBIOT) has been founded. The Ministry of Science and Technology is the governmental body which supports biotechnological development in Spain, together with institutions like the National Centre for Biotechnology (Centro Nacional de Biotecnología - CNB), universities, hospitals, etc. The results achieved in the year 2000 regarding scientific research and technological development (R&D) have been collected in the form of basic indicators by the National Statistics Institute (Instituto Nacional de Estadística - INE). However, these indicators do not establish biotechnological development as a separate speciality from R&D.

The ASEBIO report, carried out in 2000, was the first report published in Spain referring to the biotechnological sector. According to this report, the Spanish biotechnological sector has over 200 companies, though in 64% of cases, this activity does not appear as being the companies' main activity. These companies have the following profile: they are young, highly innovative companies with a marked vocation in exportation. Specifically, they are small or medium-sized companies (with fewer than 500 workers) with recent experience in this field (81% began their activity in biotechnology less than 25 years ago), mainly of national ownership and in more than 50% of cases selling to European markets.

With regard to the employment generated in this sector, according to the same report, companies in biotechnology provide employment for 25,000 workers in Spain. In recent years, there has been a growing tendency regarding the number of employees and personnel involved in research. They are also companies that have intense knowledge (52% of human resources have higher degrees/diplomas and 9% of the staff is devoted to research and development) and they are companies that are innovative (40% of companies have developed new products in the last two years). On the other hand, the growth in the number of employees and researchers has also affected aggregate turnover, which amounted to almost 4,450 million euros in 1999, 13% more than for the previous year.

As far as the weight of each sector is concerned, their heterogeneity is noteworthy, but food and agriculture is notable (45%), followed by human health (17%) and the environment (12%).

4.2.1. Distribution of the Spanish biotechnological market

Currently, more than 50 universities, technological and research centres are working in the field of biotechnology in Spain and have superb studies published in the most prestigious international journals. The Spanish bioindustry, which is composed of more than 200 companies, is present and especially competitive in such sectors as human and animal health, followed by the food and agriculture sector and the environment. Due to its high potential for innovation, the degree of internationalisation and the volume of exportations by Spanish biocompanies are growing all the time. The financing system is becoming more and more aware of the possibilities of this rapidly expanding sector and active mechanisms exist for the creation of start-ups and the financing of novel projects.

As far as the available information on biotechnology is concerned, the Spanish society has an adequate degree of information thanks to the specialised press and to consumer associations with the capacity to analyse and a high degree of responsibility.

4.2.2. The Spanish Association of Biocompanies (Asociación Española de Bioempresas - ASEBIO)

The Spanish Association of Biocompanies (ASEBIO)[17] includes over 60 companies, associations, foundations, universities, technological and research centres that either directly or indirectly carry out their activities relating to biotechnology in Spain. In the international field, the ASEBIO forms part of EUROPABIO, the European Association of Biocompanies, which is made up of more than 12 national associations representing over 800 European biotechnology companies.

The broad base of associates makes the ASEBIO the most suitable meeting point to be able to defy the challenge of developing the biotechnological sector and take advantage of the opportunities for innovation presented by biotechnology as a vector of economic and social growth in Spain.

The ASEBIO is committed to Spanish society in the development of the national biotechnological scene. With this aim, it closely collaborates with national and European administrations, as well as with all those social organisations that are interested in the use of biotechnology in order to improve the quality of life, the environment and the creation of qualified employment. Its main aims are:

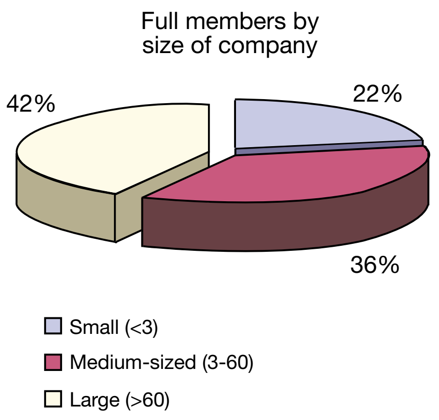
- to defend the interests of its associates,
- to develop the biotechnological market in Spain,
- to collaborate with the national and European administrations in the development of a legal and institutional framework promoting innovation in the sector,
- to boost international marketing of the Spanish biotechnological industry,
- to promote scientific research and technological innovation activities,
- to support biobusinessmen and the creation of small and medium-sized biotechnological companies,
- to promote the permanent analysis and study of the sector and its tendencies both in Spain and internationally,
- to promote the dissemination of scientific-technological breakthroughs in biotechnology and the benefits it can give to society.

Companies belonging to the ASEBIO

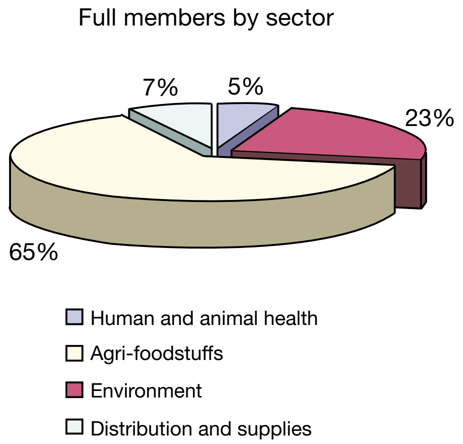
Biotechnology is horizontal in nature due to the breadth of scientific and technological know-how that it is made up of and the diversity of applications it has in different sectors. Thus, at the ASEBIO, companies come from all sectors: human and animal health, agriculture, food, the environment, distribution, supplies and bioprocesses (figure 2).

[17] Web site: http://www.asebio.com

Figure 2
DISTRIBUTION BY SECTORS AND SIZE OF COMPANY OF THE ASEBIO ASSOCIATES



In millions of euros



Moreover, the ASEBIO is made up, among its founder members, of the most prestigious universities, R&D centres and technological centres in Spain, as well as a variety of foundations and business associations. This Association is thus becoming the ideal scenario for interaction to take place between science, technology, the market and citizens.

Types of ASEBIO associates

The ASEBIO is made up of different companies and institutions, which are split for organisational purposes into two categories:

- **Full members.** Companies dealing in, related to or that use biotechnology in the fields of research, development, innovation, production, distribution or the marketing of products and/or services. These companies make up 23% of the membership.
- **Associate members.** Organisations whose activities are related to those carried out by the full members. 77% of members belong to this category.

ASEBIO 2000 Report

The ASEBIO 2000 Report, the first in Spain on the biotechnological sector, gives an overview of Spanish biotechnology. It includes the opinions of over 100 companies, 50 institutions and 60 national venture capital institutions. Experts in legal, social, scientific-technological and financial affairs all contributed to its writing. All of them designed the ASEBIO Index which analyses the "temperature of the sector", identifying the current situation and its main trends. Likewise, there is also a Who's who directory in biotechnology, 100 regulations on biotechnology and 300 websites are referred to.

Below is a summary of the subjects dealt with in the report in question.

Current situation and background

According to the data in the ASEBIO 2000 Report, biotechnology in Spain turns over some 740,000 million pesetas.

In December 2000, the biotechnology sector in Spain included over 200 companies, which jointly turned over more than 4,448 million euros employing over 25,000 workers.

Barring the limitations of generalisation, the typical company in this sector in our country has fewer than 500 employees on its staff, has recently begun its activities (81% are under 25 years old), is located in Madrid and Catalonia (half of the companies in this sector are located in these two regions), predominantly exports and is intensive in human capital (52% of staff have a degree/diploma) and is highly innovative and highly dynamic.

These companies are principally involved in human and animal health matters, food and agriculture, distribution and the environment, and develop their activities in several subsectors of biotechnological application. Furthermore, these are companies that export half of what they produce and they are highly innovative (40% have developed new products in the last two years and spend 4% of their turnover on R&D).

Normally, biocompanies belong to Spanish businesspeople and in the last two years, one in four companies has carried out alliances, a merger or a take-over in order to form groups that gain in dimension and competitiveness in the national and international markets.

Biotechnology has aroused a growing interest among investors, which can be seen when considering that 25-30% of venture capital companies have invested in this sector in the last three years.

Spain has a long-standing tradition in the field of biology, dating back to the beginning of the century with the work done by Santiago Ramón y Cajal. Biotechnology surged in the eighties with the will to become integrated into the scientific and business world through the proactive policies of the administration. In the 21st century, Spain entered into biotechnology with a system of innovation with important scientific-technological and business strong points based on co-operation between the private and the public sectors.

Business framework

Due to its horizontal, multidisciplinary nature, the biotechnological market possesses a different structure and competitive key points according to the subsector in question. The commitment by business to the use of biotechnologies is causing, due to the need to create synergies, mergers or take-overs, which means that chains of value that have been clearly differentiated until now, such as human health and food and agriculture are converging.

The large number of mergers and take-overs that take place concerning technological platforms are shaping a “virtual” business model in which many opportunities arise for medium-sized companies to compete globally. The beginning of similar processes can be appreciated in the case of Spain (alliances, mergers and take-overs) which may be advancing the development of a business model in which intercompany co-operation and synergetic management will be a key factor for success. The recent evolution of the Spanish market allows the indication of a clearly increasing tendency towards growth as far as turnover, the number of companies and the number of employees are concerned.

From an economic-financial point of view, the Spanish biotechnological sector has some positive parameters regarding: the growth of profit, the reasonable leverage index and the good profitability of net assets and own resources.

Institutional framework

Throughout the last two decades, biotechnology has been a priority of R&D policies, both on a national and a European scale. Policies have pursued the promotion of basic research in biotechnology and the collaboration between the public and private sectors. Initiatives on a regional scale are still quite unspecific regarding biotechnology, though the trend seems to change with the appearance of proactive policies in different regions of Spain.

Legal framework

Biotechnology is one of the most strictly regulated sectors in existence, despite the commonly held belief in society in general. Regulation is particularly marked in such subsectors as human health, animal health, agriculture, food and the environment, which are those that have the greatest political and socio-economic importance. The subsectors of supplies and equipment and distribution share regulation with the first five subsectors with which they relate. It is the European level that offers the greatest number of regulations and standards concerning biotechnology and its applications, followed by the national and regional scales.

Social framework

The advances in research into life sciences face a highly complex social reaction. The social perception of these advances reflects a mixture of worry and lack of information combined with the presence of cultural elements and certain ethical and social values. Despite this, in most surveys conducted by Eurobarometer, the Spanish are among the most optimistic with regard to biotechnology and its applications, although at the same time, little social debate takes place on such matters.

R&D Framework

Spain has a scientific-technological supply on a level which is similar to the European average, although it still has not reached sufficient critical mass. Nevertheless, there is seen to be a high level of competitiveness in European and national programmes. The greatest concentration of human and technical resources are in the universities and the Spanish Council for Scientific Research (Consejo Superior de Investigaciones Científicas - CSIC), which is an institution that stands out due to the high concentration of human resources and activities.

Financial Framework

The scarce orientation of the Spanish financial sector towards biotechnology is a clear weak point in comparison with other countries. Despite this, and, having surveyed 60 venture capital entities, a more proactive tendency towards biotechnology has been detected as being a profitable niche for investment. Biotechnology is increasingly arousing the interest of Spanish investors as can be seen when considering that 25-30% of venture capital companies have invested in biotechnology in the last three years.

The main obstacles adduced to investment in biotechnology are: the high degree of investment with long maturity periods, the difficulty in evaluating projects with intangible assets, the lack of qualified personnel and the low number of projects that can be evaluated.

The main opportunities detected by venture capital are: a market with high growth and economic potential, a highly innovative sector with great capacity to create value for the investor.

Spain's role in the international context

Among the leading countries are the United States, Japan, the United Kingdom, Germany and France. The United States stands out because of its leadership based on the existence of a large number of companies of the right size which operate a system of dynamic innovation that attracts the investors' attention where taking on risks is rewarded. Notable as being a common factor to all these countries is the existence of their Governments' proactive policy in support of biotechnology.

Mexico, Taiwan, China, India and Cuba are noteworthy emerging countries. Most are developing countries and they aspire to position themselves in specific niches of the biotechnological market throughout the world as an instrument to help them take off economically and socially.

Spain can play a relevant role in the international arena if it takes advantage of strategic opportunities such as the following: acting as a business and cultural bridge in the existing triangle of Europe, the United states and Latin America; promoting the internationalisation of the Spanish biotechnological sector taking advantage of the existing commercial, institutional and diplomatic networks, and taking advantage of Spain's scientific and technological potential to create companies of a sufficient size as to be able to compete in a global marketplace.

Conclusions

Biotechnology is recognised by experts as being a sector in the new economy with a capacity to act as a vector of economic and social growth for those countries that promote its development. Indeed, the biotechnological sector is being confirmed as an area of business activity in which companies can be firmly established based on technology and qualified employment.

The use of biotechnology in traditional sectors is allowing processes of innovation where mature technologies were unable to face the challenge of innovation. And, moreover, biotechnology is providing horizontal value to its different subsectors of application, in such a way that a conversion process between chains of value, which until now were very different, is being favoured, such as human health and food and agriculture.

From the structural point of view, on a world scale, the sector is currently being restructured, with a great many mergers and take-overs shaping a virtual business model. This model is timidly starting to be appreciated in the case of Spain, where businesses are starting to merge and take-overs are being carried out even between companies of different subsectors.

The turnover of the Spanish market is growing (a 13% increase in the turnover for biotechnology between 1998 and 1999) and is currently approaching 4,448 million euros, just as the number of companies (currently estimated at 200) as well as the number of employees (from 22,825 to 24,197 for the period 1998-1999).

Let us recall that the average profile of a Spanish biotechnology company has the following characteristics:

- A medium-sized company: fewer than 500 employees.
- With recent experience in the field of biotechnology: 81% began their activity in this field less than 25 years ago.
- Preferably located in Madrid and Catalonia: these two regions hold 50% of companies.
- Principally nationally owned: 63% of companies.
- Export vocation: over 50% of companies export to Europe.
- Highly innovative: 40% of companies have developed new biotechnological products in the last two years, spending an average of 4% of their turnover on R&D&I (Research, Development and Innovation).
- Know-how intensive: 52% of human resources possess a degree/diploma and 9% of the staff performs R&D tasks.
- Highly dynamic with a very high percentage of partnerships or processes of mergers or takeovers: 26% of companies in the last two years.
- Multisectorial: more than 50% of companies operate in more than one subsector of biotechnological application.

In economic-financial terms, the Spanish biotechnological sector shows positive results, among which the most notable are a greater growth in profit for the two year period 1998-1999 compared to the average profit for Spanish industry, with a good leverage index and net worth and own resources yield tending to rise in this two year period. Furthermore, the future need for financing in order to tackle growth and the increasing expenses involved in innovation augur a greater appearance on the stock exchange of small biotechnology companies in the coming years. Contrarily, company size is lacking, which diminishes the ability to compete in global markets and there is insufficient critical mass for the development of innovation capacities as a competitive key in the biotechnological sector.

In the sphere of public policy, great interest can be appreciated by the administration in boosting the Spanish biotechnological sector, both on a national and a regional level, though the initiatives taken to date, though praiseworthy, still have a long way to go in comparison with the clear backing other European countries are giving to biotechnology.

Following an international comparison, the existence of specific structures promoted by the Governments of different countries can be appreciated whose administrations promote and co-ordinate the necessary activities to boost the development of biotechnology. This may reveal the need to get similar platforms under way in our country to act as executing and co-ordinating instruments of proactive public policies in the field of biotechnology. In the coming years, regulation shall play a fundamental role in the development of the sector, in which the European Commission is the administration setting the guidelines to follow within the legal framework.

The importance of scientific dissemination and information supplied to the citizen is seen as being a key aspect in order to improve society's understanding of the scientific and technological advances made by biotechnology.

The great majority of companies (87%) finance their R&D with their own resources, which would seem to suggest a need for greater reconciliation between the public and the private sectors regarding the financing of R&D&I in biotechnology, since public support for the sector is a clear differentiating element between leading countries and followers in a global market.

The world of finance and venture capital seems to be taking its first steps towards investing in biotechnology in Spain. Surveys show a clear improvement as regards the intention to invest in biotechnology, which is seen as a sector having great potential for growth in the next few years. Despite this, the current situation is a long way from that of other countries, where biotechnology has greater weight in the project portfolio of venture capital investors.

In an international market dominated by the United States, Japan, the United Kingdom, Germany and France, the internationalisation of biotechnology "Made in Spain" is still scarce and the Spanish market is hardly known about beyond the country's frontiers, making it difficult to attract foreign investment. To this end, international co-operation is still scarce and has a great potential for development. Thus, Spain may have an important role to play in the international arena if it takes advantage of strategic opportunities such as acting as a cultural and business bridge between Europe, the United States and Latin America.

With this outlook, the sector also presents some weak points, such as, for example, the lack of investment, both from private initiative to generate larger, more internationally competitive groups, and from public initiative, since, as previously mentioned, in most cases, biocompanies finance their R&D with their own resources.

A lack of training is also detected. Despite technical-scientific training being of a high standard in Spain, a deficit is perceived in the company management of potential biobusinesspeople, in addition to the generalisation of postgraduate studies in biotechnology at universities.

To sum up, here is a "statement of accounts" on the present and the future of biotechnology in Spain:

1. Biotechnology is recognised by experts as being a subsector in the new economy which is capacitated to act as a vector for economic and social growth for those who promote its development.
2. Biotechnology has been confirmed as an area of company activity in which technology-based quality employment companies can be set up.
3. The use of biotechnology in traditional sectors is allowing innovation processes where traditional technology is unable to face up to the challenge of innovation.
4. The turnover of the Spanish market is growing, as is the number of companies and employees. Likewise, the economic and financial results have a positive trend, some being greater than the average for Spanish industry.

Finally, it should be pointed out that the complexity of the national system of innovation in biotechnology demands and justifies the existence of a business association like the ASEBIO which backs innovation in the sector, facilitates dialogue with the public administration and feels committed to informing society as to the breakthroughs and advantages that biotechnology can contribute as a vector for economic and social growth.

The relationship between the central Government and the ASEBIO

The Minister of Science and Technology, Anna Birulés, has established a relationship with the companies of the biotechnology sector, which has meant that it has been possible to deepen collaboration between the ASEBIO and the Ministry of Science and Technology.

Moreover, the ASEBIO is noted for promoting an increase in the expenditure on research and development of the sector's companies, as well as in the boost to financing the sector through such mechanisms as venture capital.

4.2.3. The Spanish Biotechnology Society (Sociedad Española de Biotecnología - SEBIOT)

The Spanish Biotechnology Society (SEBIOT) was formally constituted in 1989 with the aim of promoting the development of biotechnology in all its branches and activities, in Spain.

The SEBIOT's main aims are to:

- promote and organise scientific meetings;
- encourage contact between biotechnologists and other scientists and technicians;
- boost research and facilitate the transmission of know-how in biotechnology;
- steer collaboration relationships with public and private scientific bodies;
- promote exchanges with other countries, especially within the framework of the EU;
- sponsor scientific publications.

4.2.4. National Centre for Biotechnology (Centro Nacional de Biotecnología - CNB)

The National Centre for Biotechnology (CNB) was inaugurated in 1992 in order to promote research into advanced biotechnology, acting as a link between basic research and industrial applications. The Centre, which has its own statutes and functioning, belongs to the Spanish Council for Scientific Research and is managed by a council at which several ministries, universities, the Autonomous Community of Madrid and industry are represented. The CNB is split into five Departments:

- Molecular and Cellular biology,
- Microbial Biotechnology,
- Molecular Genetics of Plants,
- Macromolecular Structure,
- Immunology and Oncology.

The greatest research efforts concentrate on the fields of medicine, agriculture and the environment. In particular, specific projects exist which are focussed on functional genomics and proteomics; the development of biocomputational tools; the control of cell growth and cancer; mechanisms of ageing and apoptosis; the development of animal models for chronic autoimmune diseases and infectious and tumoral diseases; the development of vectors for genetic therapy; the building of vaccines for humans and farm animals; the development of stress-resistant plants; the building of new micro-organisms for environmental recovery; the production of antibiotics and hydrolytic enzymes, and the discovery of immunomodulator compounds.

4.2.5. Spanish Council for Scientific Research (Consejo Superior de Investigaciones Científicas - CSIC)

The Spanish Council for Scientific Research (CSIC) is an important driving force for biotechnological research. Within the CSIC there are different institutes that perform basic research within whose framework biotechnological applications may be developed, but there are other institutes that directly contribute to the industrial development of bioprocesses. The Institute of Industrial Fermentations (Instituto de Fermentaciones Industriales - IFI) belongs to this last category, and it researches along the following lines:

- modifications and interactions of food ingredients, during technological processes;
- changes in the content of phenolic compounds in food subjected to different treatments: germination, fermentation, ageing, etc.;
- modification of the vitamin content and the nitrogen fraction in pulses, wines, juices and dairy products;
- selection of chemical indicators for process control;
- identification of bioactive peptides in food obtained by fermentation.

As regards the development of new methods of analysis for the characterisation and quality control of food, the IFI deals with:

- the optimisation of electrophoretic techniques (capillary electrophoresis, in ultrafine gels, electrophoretic transfer, etc.) for the detection of proteins of a variety of origins in food and for the enantioselective analysis of target molecules in food;
- the direct union between reversed phase liquid chromatography and gas chromatography (RPLC-GC) for the study of vegetable oils and of the enantiomeric composition of some compounds in food;
- the characterisation of transgenic food by means of the combined use of biotechnical and capillary electrophoretic techniques;
- the development of molecular biology methods for the detection of aminobiogenic lactic bacteria.

Within the field of the development of new processes and products, the IFI is working on the following:

- the bioechnological production of enzymes of food-related interest;
- the elimination of antinutrients in pulses;

- the extraction of compounds which are high in added value and are potentially bioactive, by means of the use of supercritical fluid technology;
- the treatment of dairy products at high pressure in order to prolong their shelf life and to improve their technological aptitude;
- the characterisation and properties of technological and biological interest of compounds that come from the hydrolysis and glycosylation of lactic proteins for their use as ingredients in functional foods.

Finally, regarding the development of microbial cultures and the molecular characterisation of microorganisms of interest concerning food, this institute is working on the following:

- microbial cultures for the making of traditional foods;
- the molecular characterisation of yeast and bacteria of oenological interest;
- the genetic modification of yeast for the production of stabilising nanoproteins and to speed up the ageing process of sparkling wines.

4.2.6. The development of biotechnology by the Spanish Government

Programa de Fomento de la Investigación Técnica - Programme for the Promotion of Technical Research (PROFIT)

The Programme for the Promotion of Technical Research (PROFIT) is an instrument of the Ministry of Science and Technology that aims to encourage companies and other bodies to develop technological research and development activities through public grants.

The PROFIT comprises the scientific-technological and the sectorial areas of the National Plan for Scientific Research, Development and Technological Innovation - Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica (R&D&I) for 2000-2003, and it is managed by the upper bodies and directors of the Ministry of Science and Technology.

The lines of aid for scientific research and for technological development included in the Government's Strategic Initiative for the Development of the Information Society (INFO XXI) are also incorporated into this programme.

PROFIT aims to:

a) Encourage the application of know-how and the incorporation of new ideas into the production process.
b) Contribute to the conditions that facilitate an increase in:
    - companies' technological absorption capacity;
    - the strengthening of the fast-growing sectors and markets;
    - the creation and development of technology-based companies, especially for high technology.

The PROFIT programme was first called by Order of 7 March 2000, which has been modified on several occasions as a consequence, on the one hand, of the creation of the Ministry of Science and Technology and, on the other, of the flexible development of the National R&D&I Plan, as an instrument evolving in accordance with scientific and technological change.

The scientific-technological areas of the National R&D&I Plan are established in the following National Programmes:

- The National Biotechnology Programme (including genomic and proteomic action),
- The National Programme on Industrial Design and Production,
- The National Programme on Materials,
- The National Programme on Chemical Processes and Products,
- The National Programme on Natural Resources National Programme of Food Resources and Technology,
- The National Information Technology and Communications Programme,
- The National Socioeconomy Programme,
- The National Biomedicine Programme (including Veterinary and *Profarma* Action).

The sectorial areas within the National R&D&I Plan are those which are covered by the following programmes:

- The National Aeronautics Programme,
- The National Motoring Programme,
- The National Energy Programme,
- The National Space Programme,
- The National Environment Programme,
- The National Information Society Programme,
- The National Transport and Town Planning programme.

The National Programme on Industrial Design and Production comprises scientific research and technological development projects and action and production systems that do not fit in with the subjects dealt with and the strategic action of the remaining National Programmes.

The National Information Technology and Communications Programme, the National Information Society Programme, the National Transport and Town Planning Programme and the Strategic Action on the Handling of Air and Airport Traffic pertaining to the National Aeronautics Programme will be managed by The Ministry of Science and Technology within its jurisdiction and within the framework of the Government's Strategic Initiative for the Development of the Information Society (INFO XXI).

Likewise, horizontal support action for the system of guarantees shall exist, which shall facilitate access to the projects and scientific research and technological development action by companies for the loans awarded by financial institutions and horizontal support action for technological centres that carry out projects and action contemplated in the national programmes corresponding to the scientific-technological and sectorial areas managed by the Ministry of Science and Technology.

The projects and action which may be eligible for aid from the Programme for the Promotion of Technical Research shall fall into the following categories:

a) **Industrial Research Programmes:** Projects oriented at basic research related to the corresponding National Programme, which shall be planned for the acquisition of new know-how that may be useful for the creation of new products, processes or technological services or contribute to the improvement of existing ones.

b) **Technical viability studies prior to industrial research activities:** Critical studies or viability studies aimed at acquiring know-how that may be useful for the creation or improvement of products, processes or technological services.

c) **Pre-competitive development projects:** Projects aimed at the materialisation of the results of industrial research into a plan, sketch or design for products, processes or services of new, modified or improved technology, for the purposes of sale or use, including the creation of a preliminary prototype which is not to be marketed. Technological diagnoses and projects concerning the improvement of the management of technical research may be included in these projects.

d) **Technological demonstration projects:** The projects aimed at the development of pilot projects or initial demonstrations derived from pre-competitive projects that are not useable for industrial applications or commercial exploitation. These projects may be developed by one or several entities, with the participation of users that intervene in the definition of specifications and the follow-up of the project. The final result of this development shall be a prototype for demonstration purposes, validated by the users and having international implications.

e) **Special action:** The dissemination, aimed at all companies in all business sectors, of the results of scientific research and technological development activities, as well as the instruments of public policies for the promotion of such activities oriented at the process of technology transfers within the science-technology-company system. Among other action is the organisation of congresses, seminars or conferences within Spain, in particular of events which have international participation, as well as action directed at the external promotion of technological development.

f) **Action in international programmes:** Action which favours the participation in different programmes: EUREKA, IBEROEKA, European Community framework programmes for research, demonstration and technological development action, as well as other international co-operation programmes in the field of scientific research and technological development activities.

g) **Socio-economic research programmes:** Studies directed at improving the quality of research, analysis, design and the evaluation of the different alternatives for economic, social and industrial policy within the framework of the progressive integration of the markets, studies aimed at identifying key determining factors of economic growth and competitiveness, the economic and social evaluation of scientific research and technological development activities, as well as determining the effects of action taken concerning quality of life, social welfare and the creation of employment.

Such types of project may be carried out in accordance with the following forms: individual project or technological action or joint project or technological action.

With regard to the National Biotechnology Programme, its aims are as follows:

a) to promote the projects and action of scientific research and technological development activities in companies related with biotechnology;
b) to promote and facilitate the development of processes based on biotechnology in companies in a variety of industrial sectors and services;
c) to contribute to the development of technology and products that can be incorporated into the market in suitable time spans;
d) to reach an international level of competitiveness;
e) to favour development in genomics and proteomics, oriented at applications of interest to human and animal health, food and agriculture and industrial production processes.

Those who may benefit from the aid included in this National Programme are:

- companies;
- groups or associations of companies;
- public research bodies;
- non-profit making private research and development centres;
- public institutions, in the case of the projects or action included in sections 1.e), f) and g) of article 3 of the corresponding Order.

The areas whose themes are considered as being a priority of this programme are:

a) biotechnology applied to analysis and diagnosis:
  - technologies of identification and genetic analysis;
  - the development of technologies and systems for diagnosis and the monitoring of human and animal diseases;
  - the development of technologies and systems to detect vegetable pathogens; the identification of vegetable varieties and breeds of animal;
  - the development of technologies and systems to detect substances of chemical or biological origin and micro-organisms for their application in the characterisation of industrial products, foods, effluents, etc.;
  - the development of biosensors.

b) The development of biotechnological, fermentative and enzymatic processes:
  - process engineering and control technologies and the operation of bioreactors;
  - obtaining products to be applied in human and animal health, agriculture, transformation processes in chemistry and the production of food, additives, biofertilisers, etc. through biotransformation, fermentative, enzymatic processes and other processes of bioremediation;
  - extraction technologies and systems and the purification of substances.

c) The genetic improvement of micro-organisms, plants and animals:
  - Technologies for genetic improvement, transformation, multiplication and in vitro cultures of plants of interest for agriculture and forestry;
  - Technologies of reproduction and genetic improvement of animal species of economic interest;
  - Microorganisms of industrial interest to be applied in fermentative processes, starter cultures, the obtaining of substances, etc.

d) Action in genomics and proteomics:
   - Structural and functional genomics of genes and genomes of interest in human and animal health, agriculture, livestock and industrial production processes;
   - Proteomics oriented at the development of biological proteins and molecules of interest in obtaining products for their application in health, food, etc.

EUREKA Programme

This European R&D initiative is consolidated as a principal tool for European business innovation.

The Ministers and representatives of the 26 EUREKA countries, plus the European Community Commission, which met at the XVIII EUREKA Ministerial Conference (Hanover, 23 June 2000), adopted the *EUREKA 2000+ document. Principal Lines of Action.* At this event, Spain took on the role of presiding the programme: the top position in the EUREKA hierarchy has meant that Spain was able to propose and start up the forthcoming strategic lines in R&D issues for European industry and services.

In Hanover, the heads of EUREKA highlighted the importance of this European initiative for co-operation in R&D&I, as much for its effort since 1985 as for the primordial role that the Area of European Research should have in the future. Among other matters, the need to internationalise SMEs was insisted upon, as was the importance of the exchange of information concerning the respective systems of national financing.

The *EUREKA 2000+* document aims to stimulate the generation of projects through support and financial backing measures for international co-operation in R&D and the possibility of the improved co-ordination of the different national systems of financing was suggested, when considering, for example, the creation by the different members of a financial instrument for international co-operation.

This ministerial conference passed the applications made by Israel, Croatia and Latvia to become new EUREKA members, which thus has 30 members. Also officially announced was the passing of 164 new EUREKA projects to the value of 406 million euros. According to these data, 40 projects with Spanish participation were approved, and so Spain was situated in third position within the range of countries as for the volume of participation and second as regards projects led. Such Spanish participation involves a total investment of some 48,1 million euros.

The Centre for Industrial Technological Development (CDTI) —affiliated to the Ministry of Science and Technology which, commissioned by the latter, oversees the EUREKA programme in Spain— has created the EUREKA programme office, which now channels all matters regarding this Presidency.

It should be remembered that since its beginnings, EUREKA has been a priority programme for the Spanish administration, which has given it preferential treatment as far as financial aid is concerned. In particular, the Ministry of Science and Technology, through the PROFIT initiative, offers industries subsidies of up to 35% of the project budget and the CDTI finances companies participating in EUREKA Projects with interest-free loans to be paid off over an eight year period, which cover up to 60% of the project budget. Concerning the main technologies involved in the Spanish projects, 12 deal with biotechnology and food and agriculture, 11 with information technology and computing, 8 with new materials and robotics, 5 with the environment and 4 with transport and energy.

Habitually, Spain has participated in all strategic EUREKA projects: EURIMUS (devoted to microsystems), PIDEA (packaging and interconnection development in microelectronics), ITEA (middleware, mass software for applications) and SCARE (recycling of electronic systems). Moreover, Spain leads two of these large projects: ANGEL (which concerns the location and deactivation of antipersonnel mines) and EUROFOREST (whose aim is to produce species of hardwood trees through the use of new advanced growing techniques). Both projects, in which over 50 organisations from 25 countries have participated to date, have aroused great interest throughout the EUREKA network. Taking advantage of Spain's Presidency of the European Union, Spain wishes to initiate a new strategic project devoted to technology in the tourism and leisure sector, via the EUROTOURISM project.

4.2.7. Interaction between the central Government and the autonomous communities in the promotion of biotechnology

On 16 July 2001, the Minister of Science and Technology signed a Framework Agreement with the president of the Junta de Castilla y León (Government of the region of Castilla y León) concerning scientific research, development and technological innovation, with the common aim of promoting the development of excellence in research which would contribute to the advancement of know-how and raise the technological level of companies to improve citizens' quality of life and increase companies' competitiveness. This is the second Framework Agreement signed by the Ministry of Science and Technology with an Autonomous Community, further to the one signed with the Xunta de Galicia (Government of the region of Galicia), last June.

In order to achieve the objectives pursued by the Framework Agreement, both the Ministry and the Junta shall start up promotional action for research activities, the National R&D Plan and the Castilla y León Regional Technological Plan. Both parties agreed as to the need to promote the creation of critical masses in order to tackle the challenges posed by Spanish research, to pave the way for the internationalisation of Spanish business groups, especially in the context of the European Research Area, to increase the quantity and quality of human resources in research, contribute to the transfer of technology to the business sector and scientific and technological dissemination.

Joint co-operation action shall concentrate on the following areas: biomedicine, biotechnology, chemical products and processes, food and agricultural resources and technology, food, motor, telecommunications and aeronautics.

4.2.8. Improvement of the legal framework for the promotion of innovation in Spain

On 27 March 2001, the Minister of Science and Technology, Anna Birulés, stressed the substantial improvement that has come about in the legal framework for the promotion of innovation in Spain.

At the Forum on Competitiveness in Business - Innovación 2001, the Minister pointed out that in recent months, a general legal framework had been consolidated which should allow an increase in the innovation activity in Spain and she also mentioned as one of the most important measures of this framework "the substantial promotion of fiscal incentives for innovation, increasing deductible concepts and the percentages deductible". Also, the Minister of Science and Technology said that this improvement has increased "the existing fiscal incentives for R&D and new incentives have been introduced for technological innovation". Thanks to these measures, the fiscal treatment of technological innovation in Spain is now the most favourable in Europe.

Likewise, the Minister highlighted a series of macroeconomic conditions within this general legal framework favouring innovation, such as budgetary stability and the containment of inflation, the freeing of markets, and specific laws to inspire society with confidence in the face of the challenges posed by new technologies concerning such aspects as data protection and privacy, consumer protection in e-commerce, advertising, and intellectual property.

Finally, the Minister mentioned that the Programme for the Promotion of Technical Research (PROFIT) is one of the Ministry of Science and Technology's main tools for the promotion of innovation, within the general framework of the resources that the Government awards to R&D activities, which surpassed 3 million euros in 2001.

Among the programmes associated with the projects that were finally approved by the PROFIT in the year 2000, and which have given rise to the greatest volume of investment, the most notable are those carried out in the following sectors:

- biomedicine (*Profarma* Action), with 208 million euros of investment associated with the approved projects;
- materials, with 184 million euros;
- the handling and treatment of waste, with 178 million euros;
- chemical processes and products, with 144 million euros;
- motor industry, with 115 million euros;
- material for rolling stock, with 55 million euros;
- food and agriculture, with 40 million euros;
- biotechnology, with 36 million euros.

4.3. BIOTECHNOLOGY IN FRANCE

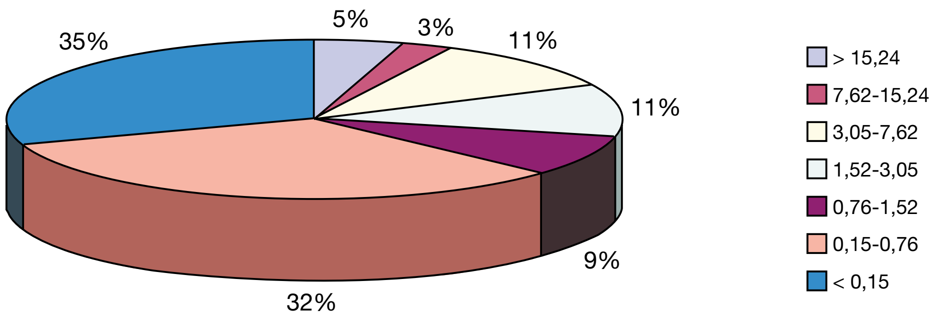
Biotechnological development in France has become a veritable industrial boom. In the year 2000, this country had almost 250 biotechnological companies and was in third place in Europe for the creation of biotechnological companies.

The biotechnological industry appeared in France in the eighties, but over 80% of biotechnological companies were created after 1990. As of 1997, and more clearly since 1999, there has been a boom of young biotechnological companies throughout France[18].

[18] For further information, please consult France Biotech (http://www.france-biotech.org).

Several of the companies created in the eighties are now solid companies of renown prestige on a world level and are leaders in the field of genomics, genic therapy, microbiology and medical diagnostics. The companies that were created later (as of the nineties) have principally been favoured by better economic and financial conditions (such as a variety of financial measures, the movement of capital on the stock exchange and the new markets). Another contributing factor has been the attitude towards companies involved in research and the attention they receive from the Government, given that a series of financial and structural measures has been established to support them. For all of the above reasons, recently nearly a hundred new biotechnological companies have been set up in France (figure 3).

Figure 3
DISTRIBUTION OF FRENCH COMPANIES RELATED TO THEIR CAPITAL
Source: Ministry of Research (1998)



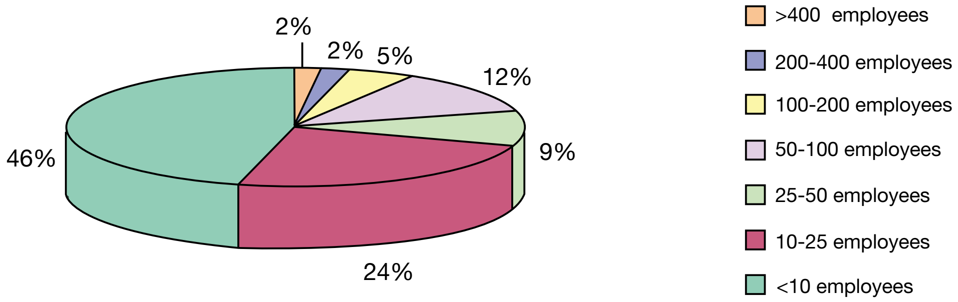
In millions of euros

Most of these young companies are innovative at their beginnings or are service companies with high added value and many have still not reached the state of commercialising their products and rendering their services. However, they can operate simultaneously, that is to say, generating and marketing biotechnology.

4.3.1. The state of the French biotechnological company

The pharmaceuticals industry has contributed significantly to the establishment of biotechnological companies in France, and the importance of this is the distribution of companies throughout the country. In fact, a network of innovative companies has been established throughout the country, which gives rise to the references to biopoles in order to stress the regional character of biotechnological development. The biotechnological biopoles have special characteristics and their own dynamics which give rise to their ability to facilitate interaction between different business-people or researchers for the creation of companies and the transfer of technology via infrastructures, services and suitable conditions to initiate the growth and development of biotechnological companies. In this respect, the existence of these biopoles has a positive result.

Figure 4
DISTRIBUTION OF FRENCH COMPANIES ACCORDING TO THE NUMBER OF EMPLOYEES
Source: Ministry of Research (1998)



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All biotechnological companies are encompassed in these biopoles, but another kind of division may be made. For example, when speaking about French companies which specialise in genomics and postgenomics, one must remember that these companies are distributed across eight regions in France which receive the denomination of genopoles: Paris, Lille, Strasbourg, Lyon, Grenoble, Marseilles, Montpellier, Toulouse and Bordeaux.

The distribution of biotechnological companies in all regions of France is a positive fact when support is distributed by the central Government and the regions. However, there also exist regions with unique biotechnological companies due to their specialisations; for example, biotechnology in plants is concentrated in the regions of Clermont Ferrand, Nantes and in Picardie.

4.3.2. Sectors of the French biotechnological industry

The dynamics of the biotechnological industry in France has been concentrated in the field of human health. Almost 70% of biotechnological companies develop their activities in applications related to human health (table 1). Specifically, the biotechnological sector, which deals with food and agriculture, covers some 20% of companies and 10% of biotechnological companies work in the fields of protecting the environment, cosmetics and other industrial applications, according to statistical data for the year 1998.

Table 1: Distribution of biotechnological companies by specific activities in the field of human health

Activity	% of companies
Antisense DNA	1.3
High resolution screening	4.1
Combinatory chemistry	4.1
Structural genomics	6.8
Vaccines	9.4
Reactives	10.8
Pharmacogenomics	12.2
Cellular therapy	13.5
Genic therapy	16.2
Therapeutic proteins	16.2
Others	18.9
Subcontracting	18.9
Vectorisation and liberation of medicines	21.6
Functional genomics	24.3

Source: Xerfi (survey in 2000).

Biotechnological activity in the sector of human health is so important in France that it is still expanding. In 1999, this sector experienced a 25% increase, to a great extent as a consequence of a greater foreign market for French products. The growth of biotechnological companies in the health sector is very fast indeed. In 1999, the whole French biotechnological industry turned over 2,000 million euros (some 13 million FF) and the health sector turned over 300 million euros, representing an increase of 20% in comparison with 1998. For the year 2001, 30% growth was estimated, and the average growth of 5 consecutive years in the sector of biotechnology related to health was estimated at 28%, which is very fast, not just in France, but in any other country.

Another good indicator of industrial activity in biotechnology is the number of patents registered. Between 1995 and 1998, the French patents office (INPI-OST) informed of the following:

- 20% of the companies that have registered a patent were set up less than 10 years ago.
- 21% of companies that have registered a patent belong to the pharmaceuticals industry.
- 32% of biotechnological patents correspond to the pharmaceuticals sector.

In practice, the French biotechnological industry has reached maturity. An indicator of this is the self financing of their research and development programmes by 60% of companies, thanks to the rendering of services and licences that have been obtained through the development and research of their own technological platforms.

Financial data such as capital invested (despite being a risky investment) in the biotechnological industry prove the sector's maturity. In the field of biotechnology related to life sciences, 200 million euros were invested in the year 2000, and so the capital of biotechnological companies was

1,900 million euros at the end of the same year. The increase in the number of biotechnological companies meant that in 1997, France Biotech[19], an association for the biotechnological industry, was constituted.

France Biotech is actively working to introduce economic and regulatory changes to benefit the industrial sector based on biotechnology and also represents and promotes the biotechnological sector and the creation of companies. In order to do so, it drafts proposals and recommendations for the French Government. On the other hand, France Biotech is an international reference point for business contacts and exchanging ideas and establishing relationships for collaboration between companies. It manages to achieve these aims through its interaction with similar associations in other countries.

The sphere of action of several French biotechnological companies is international. This tendency has been achieved through mergers with companies in the United States and with academic bodies, through research groups of different universities. This characteristic that describes the consolidated biotechnological company is also a consequence of the pressure of competition on a world scale and of the accelerated growth of new companies. It could be described as a new strategy in company development plans, which are key for the new biotechnological companies, known as second generation companies.

A clear example of this international situation is the company Genset, which was created in the nineties. Genset started off with the production of oligonucleotides, at the same time as these macromolecules are consumed in large quantities by the same company in its research activities. Currently, the Genset Oligos division is world leader in the synthetic production of DNA and has branches in the United States, Japan, Singapore and Australia. Genset wishes to attain the same international achievements with its genomic research. Its research centre is located in the Evry genopole, near Paris, and its second centre is in La Jolla (California, United States), where its research teams are working on genomic physiology, epidemiology and biostatistics. Genset has signed a series of agreements with pharmaceuticals companies such as Abbot, Pharmacia & Upjohn, Janssen Pharmaceutica, Sanofi-Synthelabo, Genetics Institute (AHP), Wyeth-Lederle Vaccines (AHP), Algene Biotechnologies Corp. and Ceres. Its academic collaborations include centres such as the Medical School of the Johns Hopkins University, the Whitehead Institute and the Atomic Energy Commission (AEC).

4.3.3. Reasons for the development of biotechnology in France

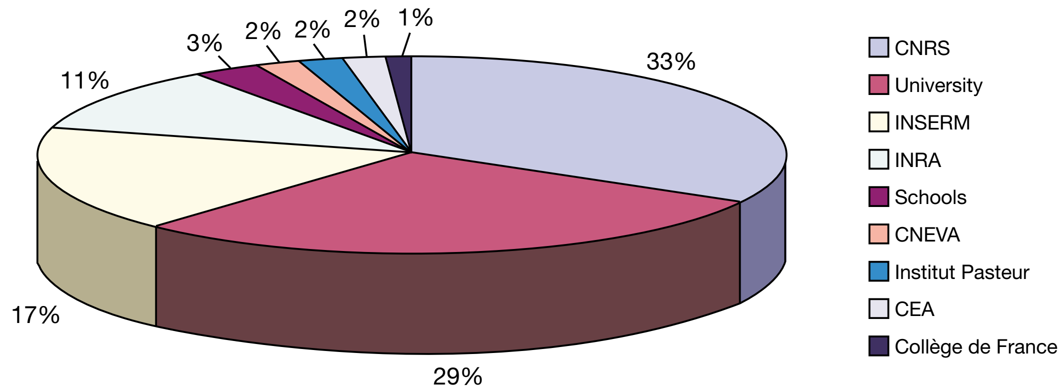
The huge biotechnological development by French companies is a consequence of several favourable conditions, one of which is that traditionally France has had an excellent standard of research. Therefore, the creation of biotechnological companies in France is the fruit of natural dynamics. The first biocompanies —the first generation that arose naturally as a result of the dynamics of research itself— allowed the creation of an atmosphere which encouraged the development and creation of new biotechnological companies. In short, we could say that the factors that explain this development are as follows:

[19] Web site: http://www.france-biotech.org

• the excellence of scientific research in France,
• the central Government and local institutions' implication in the creation of biocompanies,
• the presence of suitable sources of financing (investment capital, market, etc.).

Today, France has the necessary human and financial resources for the development of biotechnological companies, from the creation of new, small companies, to their finance, and so to consolidate existing companies and develop their international level.

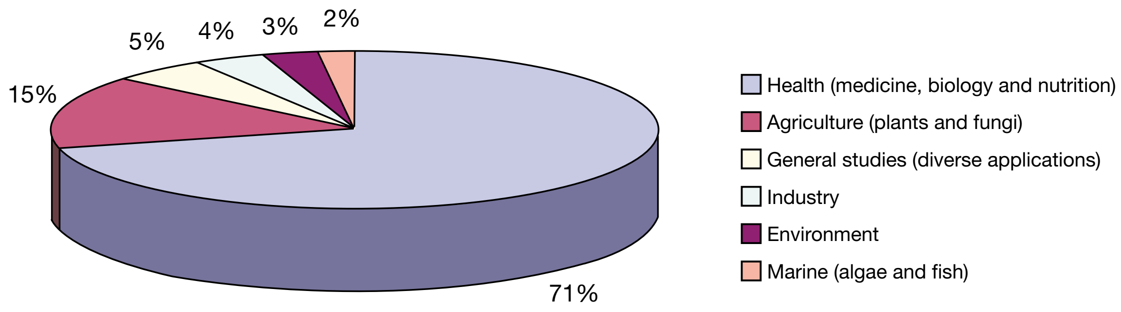
Figure 5
PUBLIC BIOTECHNOLOGICAL RESEARCH IN LIFE SCIENCES
Source: Ministry of Research (1988)



The existence of institutions of recognised international prestige constitutes a favourable situation for the development of biotechnological research in France (figure 5). These institutions are: the CNRS (National Centre for Scientific Research), the INSERM (National Institute of Health and Medical Research), the INRA (National Institute of Agronomic Research), The Institute Pasteur, the CEA (Commission for Atomic Energy), the IFREMER (French Institute of Research for the Exploitation of the Sea) and the CNEVA (National Centre for Veterinary and Food Studies).

In 1999, the CNRS awarded 457 million euros to life sciences. Its studies tend to be interdisciplinary, which means that the work is developed by several teams in a multidisciplinary manner, and so results are better valued. In the CNRS there are 5,600 people working on life sciences, one of the priority lines of both the CNRS and other institutions (figure 6).

Figure 6
RESEARCH AT RESEARCH CENTRES BY AREA OF SPECIALISATION
Source: Ministry of Research (1998)



4.3.4. Legislation that favours innovation

France has recently introduced a set of measures and incentives to reinforce the transfer of technology and the creation of innovative companies.

Law on Innovation and Research

The Law on Innovation and Research, of 12 July 1999 (Law 99-587), favours the creation of companies by researchers. This Law has 4 main areas:

- **To facilitate the incorporation of researchers into industry.** Researchers, teachers/researchers and young doctors can start and/or take part in the creation of a company in such a way that their research is taken advantage of and, at the same time, they hold a job in the public sector. Moreover, for a specific period of time, the research staff can take part as associates or take on managerial functions in new companies. Once this period has finished, they shall have to choose between returning to the public sector and remaining definitively in the company. This research staff can also carry out the role of consultants or act on these companies' boards of administration.
- **Co-operation between the public and private research sectors.** This co-operation allows the development of commercial and industrial activities such as services, the administration of research contracts or the administration of public sector organisations. The Law also simplifies administrative procedures and the signing of contracts between research bodies, universities and companies.
- **Reduction of taxes for innovative companies.** The Law has allowed a reduction in taxes (via BSPCE - Bons de Souscription de Parts de Créateur d'Entreprise and the FCPI- Fonds Communs de Placement dans l'Innovation) and has created a loan that favours research (Crédit d'Impôt Recherche). The aim of these fiscal incentives is to promote the creation of companies by young researchers.
- **Legal framework for innovative companies.** The aim is to benefit all innovative companies, including recently created companies, although they are considered as being of high business risk.

The Bioincubator Programme

The natural dynamics of the biotechnological sector in France in recent years is a consequence of the creation of a most comprehensive programme in which both the public and the private sectors participate in order to help in the creation of new biocompanies. The Bioincubator programme offers support for projects regarding their execution, supervision and financing and also provides the new companies with space for offices or laboratories (called incubators) until they find their own location as innovative companies, that is, they are bought by an existing company. These incubators are located within or near scientific facilities. For this reason, they are closely related with the research laboratories where their creators could work (researchers, teachers-researchers or young doctors). Additionally, the use of scientific and technical facilities is permitted. The assessment of projects is very broad and even encompasses the study of the possible patenting of their technology or marketing, market research, business plan or advice concerning human resources.

The French Government backs some 29 incubators, 10 of which are bioincubators. The latter recently formed the federation of bioincubators, with the aim of improving the exchange of information and experience and integrating them into a European network.

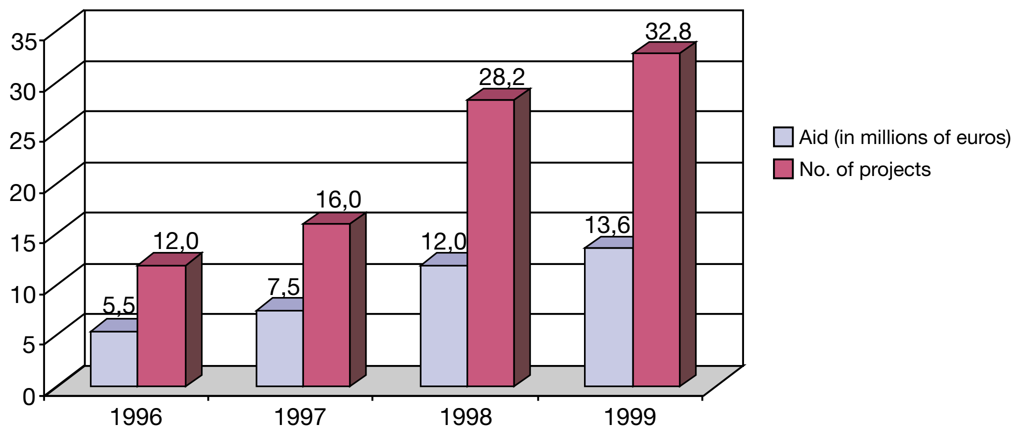
4.3.5. The financing of biotechnology

The financing of biotechnological companies has always been critical in conditioning its development. The innovation of these companies tends to make them unattractive for obtaining investment or financing from traditional sources. Biotechnological companies spend between 30% and 130% of their capital (when they have it) and the investment requires between 5 and 10 years to generate profits. Therefore, this type of high-risk investment presupposes the existence of an adequate financial structure for biotechnology.

ANVAR (National Agency for the Promotion of Research)

The ANVAR is a public body which answers to the Ministries of Industry and Research. Its function is to subsidise biotechnological companies and it is considered as being a source of aid having industrial and commercial characteristics. Its annual budget is of some 213 million euros. This not only allows it to finance small and medium-sized companies and laboratories, but also innovative development projects. Thus, the ANVAR offers several kinds of aid: the development of innovative technology, viability studies, contracting for innovation and initial support in the creation of companies.

Figure 7
ANVAR AID FOR THE PHARMACEUTICAL BIOTECHNOLOGICAL SECTOR
Source: France Biotech



The ANVAR mainly supports small, young companies. 57% of the total aid awarded goes to companies of less than 10 years' existence and 52% of the companies that receive ANVAR subsidies have only 10 employees. Aid for contracting doctors is an important part of the help needed by the sector: such aid totals 3 million euros. During the period between 1996 and 1999, the ANVAR helped in the creation of 44 companies in the pharmaceuticals sector.

Post-Genome Projects

Since 1999, the Ministry of the Economy, Finance and Industry and the Ministry of Research, in collaboration with the ANVAR made a call for the presentation of "Post-Genome: After Genome Sequencing" projects. This programme has a yearly investment budget of 30 million euros. In 2001, projects were carried out in association with the public laboratories on the following themes of priority: biocomputing, nano-bioengineering, post-genome technologies, cancer, cellular therapy and genic therapy.

The Common Investment Fund and Initial Capital

The Common Investment Fund and Initial Capital contemplates the reality that when financing innovative companies, the initial capital is lost and cannot be recovered. The French Government set up this fund investing 30.5 million euros especially allocated to the creation of incubator companies and awarding the initial capital to support their financing.

France has also created a capital grant fund to the amount of 91.5 million euros, for which the European Investment Bank has conceded 45.7 million euros. The money is handled through the Caisse des Dépôts, and the Fund's effectiveness is due to the fact that it does not participate directly in companies. This money goes towards the Common Investment Fund (FCPR), which invests directly in small and medium-sized biotechnological companies in the pharmaceuticals sector and facilitates the growth of capital grant structures that finance the small and medium-sized innovative companies.

The FCPR, which combines public and private money, has public capital of between 15 and 30%, totalling between 3 and 14 million euros.

Three types of FCPR have benefited so far from these public capital funds:

- National funds to finance large projects that require between 5 and 8 million euros.
- Small regional funds (from 23 to 30 million euros) that finance small and medium-sized regional companies.
- Funds created for personal investments during the initial period.

Capital Investors

In recent years, the availability of capital grant funds for companies has increased considerably, and hence the biotechnological sector has been consolidated. According to a study by the French Association of Capital Investors (AFIC), money and investment increased in the field of technology by 259 million euros in 1997 and by 564 million euros in 1998. In 1999, the record figure of 1,300 million euros was reached.

One of the sectors to benefit from this increment was the biotechnology sector applied to human health or the medical sector. In 1999, 167 biotechnological projects were financed and investment reached 155 million euros. In 1998, a maximum of 198 million euros was achieved. These investments surpass the amount for 1997, which totalled just 73 million euros.

The distribution of the money from investments is 2% for initial capital, 5% for creation projects and 11% for projects after creation. Biotechnological companies like Sofinnova have handled 230 million euros, 45% of which has been channelled into life sciences and biotechnology. In 1999, Apax handled 2,000 million euros, 20% of which was spent on the areas of medicine and biotechnology and the company Atlas managed 380 million euros in the same year. Lastly, Banexi and Auriga spent 65 million euros on biotechnology, equipment and information technology, and other companies such as Genavent and Aventis devoted 30 million euros to such investments.

The Stock Exchange

The creation of new markets on the stock exchange, such as the Paris Nouveau Marché and the Easdaq (Brussels), has meant that companies without immediate profit can finance their activities with public capital negotiating stock participations. This financing mechanism is not a new one given that both in the United States and the United Kingdom, this has been a successful practice.

The Nouveau Marché was created in Paris in 1996 to allow the growth biotechnological companies (table 2), in a similar way to markets like the Nasdaq (in the US) or the Easdaq (in Brussels) allow the growth of companies in the field of innovation. The innovative companies going onto the Nouveau Marché must comply with certain, relatively flexible criteria, such as: a track record without profits, have 1.2 million euros in own funds, a balance of 3 million euros and a minimum of public supplies to the value of 1.5 million euros. 8 French biotechnological companies are quoted on the stock exchange, 6 of them on the Nouveau Marché. In March 2000, the Amsterdam, Brussels and Paris exchanges decided to merge in order to create the first European exchange, Euronext. The next step shall be the merging of technological companies in the medical and biology sectors.

Table 2: Capitalisation of biotechnological companies on the stock exchange

Company (Year created)	**Date of entry to stock exchange**	**Capitalisation 14/11/2000 Million euros**	**Activities**
Transgène (1980)	26/03/98 Nouveau Marché / Nasdaq	221	Genic therapy
Genset (1989)	6/06/96 Nouveau Marché / Easdaq Nasdaq	443	Genomics and pharmacogenomics
Cerep (1989)	18/02/98 Nouveau Marché	197	Discovery of medicines
Flamel Technologies (1990)	1996 Nasdaq	11	Controlled liberation of medicines
Chemunex (1984)	06/98 Easdaq	38	Microbiological analysis
Nicox (1996)	3/11/99 Nouveau Marché	466	Liberation of medicines, nitric oxide
Eurofins Scientific (1987)	24/10/97 Nouveau Marché	452	Bioanalysis, detection of GMOs
Quantum Appligene/Qbiogene	Nouveau Marché	5.5	Molecular biology and systems for the liberation of medicines

4.3.6. Contact addresses

Companies and institutions

Biotechnologies France
Ministry of Research Database
Web site: http://biotech.education.fr

France Biotech
38, rue Vauthier
F-92100 Boulogne
France
Web site: http://www.france-biotech.org

Ministry of the Economy, Finance and Industry
Web site: http://www.industrie.gouv.fr

Ministry of Research
Web site: http://www.recherche.gouv.fr

Innovation Funds

ANVAR (National Agency for the Promotion of Research)
Web site: http://www.anvar.fr

National Co-ordination of the Network of Genopoles

Pierre Tambourin
Genopole d'Evry
2, rue Gaston Crémieux, CP 5723
F-91057 Evry
France
E-mail: pierre.tambourin@genopole.com, md.troyon@genopole.com

Investments in France

French Agency for Investments in France
2, avenue Velázquez
F-75008 Paris
France
Web site: http://www.investinfrance.org

4.4. BIOTECHNOLOGY IN ITALY

4.4.1. Analysis of the Biotechnology market

Below we present some data to help us to understand the biotechnological market on a world scale:

- More than 250 million people worldwide have been helped by more than 117 drugs and vaccines produced by biotechnology methods and approved by the FDA (US Food and Drug Administration). 75% of all biotechnological medicines have been approved in the last six years.
- There are more than 350 biotechnological drugs and vaccines currently under evaluation in clinical trials covering a range of more than 200 illnesses, including treatment for cancer, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.
- Biotechnology has simplified hundreds of medical diagnostic tests, such as that which detects the AIDS virus, and it has facilitated the detection of other illnesses in their initial stages, thus improving treatment. Pregnancy tests, which can be undertaken at home with no medical assistance, are also the result of biotechnological advances.
- Consumers enjoy foodstuffs such as soya, papaya and corn, which are produced using biotechnologies. Hundreds of pesticides and other products are employed agriculture to improve crops and reduce dependency on conventional chemical pesticides.

- The waste produced by environmental biotechnology applications is cleaner and less harmful to the environment than chemical waste residue, due to its treatment with microorganisms and the elimination of the use of caustic chemical products. Indeed, the industrial application of biotechnology has led to cleaner technology, which in turn creates less waste and less consumption of water and energy in industrial sectors such as: chemicals, pulp and paper, textiles, metals and minerals. For example, the majority of washing powders produced in the USA contain enzymes produced by the application of biotechnology in macromolecular engineering.
- DNA fingerprinting is a biotechnological process that has drastically improved criminal investigation and forensic medicine, and has also achieved significant advances in the fields of Anthropology and Forestry Management.
- Biotechnological industries have doubled in size since 1993, and their turnover has grown from 1,220 million euros in 1993 to 3,400 million euros in the year 2000.

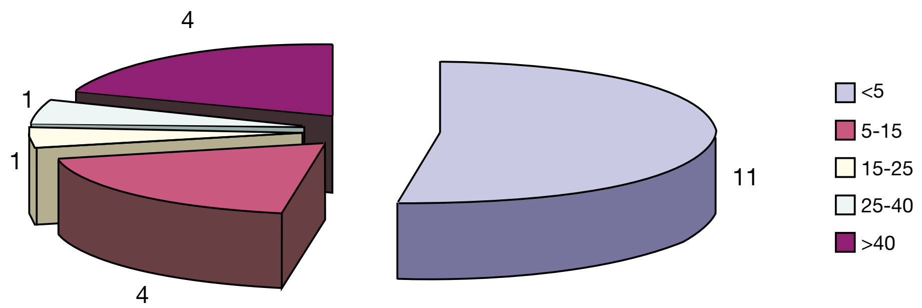
4.4.2. Business and Research

The "Biotech with Italy"[20] database allows immediate access to more than 150 research businesses and organisations along with their products, technology and/or patents. The aims of this database are to help establish commercial and technological relations and to attract capital investment. It facilitates product development and the commercial path followed by new biotech products and technologies. This database includes commercial enterprises already trading in biotech products and biotechnology, those bodies where this technology is being developed, both private and public, and even universities. The development and maintenance of the database is undertaken with the participation of specialists in the Biotech field.

4.4.3. Biotechnology companies in Italy

The levels of business undertaken by Italian biotech companies varies from the small company with a turnover of less than 5 million euros, to the established biotech company with a turnover of more than 40 million euros. (Figure 8)

Figure 8
DISTRIBUTION OF ITALIAN BIOTECH COMPANIES BY TURNOVER
Data obtained from "Biotech with Italy" (2001)



In millions of euros

[20] http://www.biotechwithitaly.com/

Italian biotech companies are involved in different biotechnological activities (see Table 3). Those companies that specialise in biotechnological activities in the pharmaceutical and diagnostic industries are the most numerous. On the other hand, there are fewer biotechnological companies to be found in the energy and animal feed sectors.

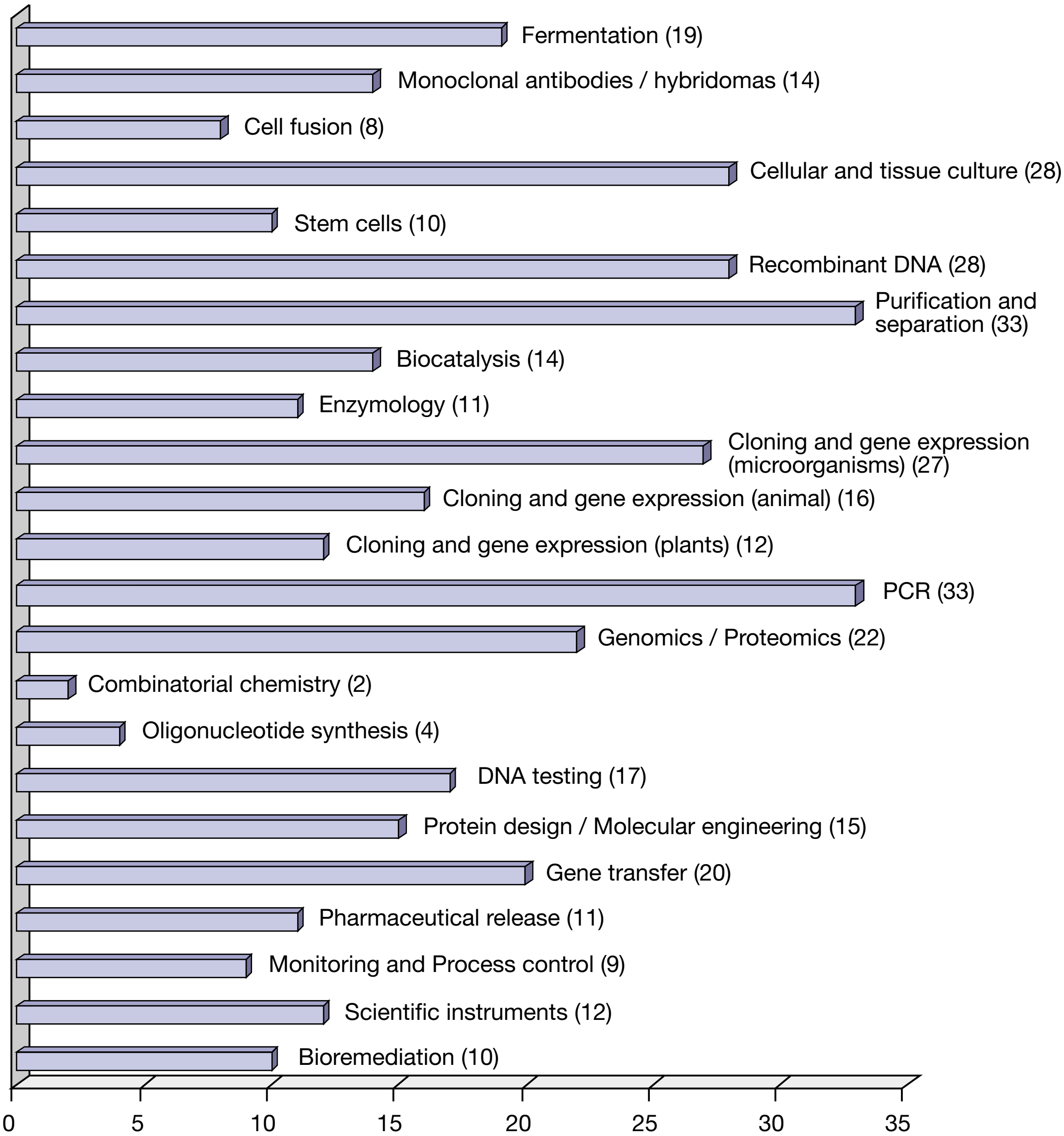
Table 3: Italian biotechnological companies by sector

Biotech Activity	Number of Companies
Pharmaceutical	
Human	27
Veterinary	8
Plants	8
Diagnostic	
Human	20
Veterinary	9
Plants	7
Agriculture	10
Stockbreeding	7
Animal feed	3
Fine chemistry	11
Food processing	7
Energy	2
The environment	19
Equipment	5
Services	13

The nature of the biotechnology activity carried out by these companies covers a wide spectrum of today's technology. Figure 9 shows a distribution by number of companies involved in each type of biotechnology.

A biotechnology firm is not limited to one type of activity alone, generally they undertake various related biotechnological activities.

Figure 9
DISTRIBUTION OF ITALIAN BIOTECH COMPANIES BY THE TYPE OF BIOTECHNOLOGICAL ACTIVITY UNDERTAKEN
The figure in brackets shows the number of companies. Source: “Biotech with Italy” (2001)



4.4.4. The Italian Institute for Foreign Trade (ICE)[21]

The Italian Institute for Foreign Trade (ICE) is a public body with a wide network of more than 100 international offices throughout the world, and its head office in Rome. Amongst the services and activities undertaken by ICE, at the forefront are: trade promotion, industrial and technological co-operation and publication of information on the Italian economy. In order to help Italian businesses to invest outside Italy, ICE also obtains and publishes economic and international market information.

[21] Web site: http://www.ice.it

In accordance with its Trade Promotion Programme, ICE organises the official participation of Italian companies in the most important trade fairs and commercial exhibitions, and also set up foreign trade delegations to trade fairs in Italy. ICE acts as the link between Italian production and overseas exports. It guides companies on export markets, sales, technical regulations, customs and taxes and currency exchange.

ICE also assists foreign companies working in Italy with advice on essential local resources.

ICE offers free information to foreign companies on the names and addresses of Italian manufacturing and service businesses data on tariffs and commercial statistics. ICE also a commercial directory listing the representatives of Italian firms.

4.4.5. Some of the centres in the field of biotechnology

Below we present three centres of interest that work in the biotechnology sector: the DIBIT research institute (Department of Biological and Technological Research - Departamento de Investigación Biológica y Tecnológica), the local biotechnological development initiative transferring technology from Milan (Biopolo) and the ASSOBIOTEC association of biotechnology companies.

DIBIT (Department of Biological and Technological Research)

The DIBIT is a research institute founded in 1992 and dedicated to fundamental research in the biological and technological areas. Its research staff is composed of 75 scientists from the University of Milan (Schools of Medicine and Biology), from the National Research Council (CNR) and from the San Raffaele Foundation, together with 120 post-doctorate and graduate students. These students are enrolled on specialised programmes or on a specific doctorate programme established by the DIBIT in collaboration with the Open University. More than 300 of DIBIT's people come from this British University, including students, technical personnel, secretaries and other service personnel.

DIBIT is made up of several research units, each one operating independently with regard to funding and research areas. Each research unit must be leader in its field, this measure is reflected in the level of its publications, which should have an average impact factor of >5.5. Current lines of research are grouped into seven areas of interest.

The scientific groups of DIBIT's research units are highly competitive, this is due to the financial assistance that they receive from generous research grants. Funds are obtained from the National Research Council (CNR) and from universities. They also receive finance from the HIV Programme of the Ministry of Health, from AIRC for cancer research and from the Telethon to study genetic diseases in Italy. Other projects are supported by the European Community and other international sources such as the Human Frontiers Foundation. These grants, in the main managed by international networks with high scientific standards, exist in place of grants to individuals, and are judged on international criteria of excellence and are evaluated by on-site monitoring. This same system of grants also supports the skilled activities of post-doctorates, which, in the main, are foreign nationals.

The field of biotechnology consists of fundamental and applied research in various fields such as: heterologous gene expression, protein engineering immuno biotechnology and biotechnological targeting.

Local biotechnological development: Biopolo (Milano), Biotechnology transfer[22]

BIOPOLO is a not-for-profit consortium, founded in January 1995 by Pharmacia & UpJohn, Lepetit Group, Zambon Group S.p.A., Primm and Hydra to promote ideas and initiatives in the biotech industry. The present shareholders are Biosearch Italia S.p.A., the Zambon group S.p.A., Primm and Hydra. BIOPOLO was formed following a feasibility study *(Biopolo Milan).* This study was undertaken at the beginning of the nineties by a promoters' committee co-ordinated by AIM (Metropolitan Interests Association).

According to its statutes, the consortium must be open to new members, from both the private and public sector. Biopolo operates from 350 m^2 of office and laboratory space located in the Centre of Excellence of Industrial Biotechnology of Milano-Bicocca (CEBIB) complex, at the Department of Biotechnology and Biosciences of the Università degli Studi, Milano-Bicocca. This Centre of Excellence was founded in 1999 by the biotech industry and its objective is to facilitate technology and innovation transfer and includes the research laboratories of the Department of Biotechnology and Biosciences, Biopolo and the 'Rita Levi Montalcini' Neuroscience Laboratory.

Biopolo is active in the development of biotechnology in Italy. It is responsible for technology transfer from university research to industry and business. Biopolo's objectives are:

- To maximise scientific research in order to:
  - Increase institucional research,
  - Improve Italy's scientific heritage.
  - Stimulate competitiveness in small and medium-sized companies.
- To create a fully equipped research centre in which toUndertake studies to identify, develop, distribute and transfer new technologies.
- To promote the transfer of new technologies by:
  - Developing basic research applications,
  - Offering support for the creation of new businesses (start-ups and spin-offs).
- To generate financial backing for research by investing in applied research processes to:
  - Enable researchers to have access to adequate equipment and laboratories.
  - Provide financial backing to establish start-up and spin-off businesses.

The operating tools at Biopolo's disposal to achieve its objectives are:

- A framework convention with the Università degli Studi, Milano (1996) y Università degli Studi, Milano-Bicocca (1999), whereby the parties introduce and administer the implementation of scientific and technological research portfolios on behalf of third parties.
- A flexible and speedy development of infrastructure, comprising various scientific and industrial bodies in the Lombardy area.

[22] Web site: http://www.biopolo.it/english/home.htm/

ASSOBIOTEC (The Association of Biotechnology Companies)[23]

ASSOBIOTEC is the representative association of biotechnology companies in Italy. Its members are new and small and medium-sized companies. The biotechnological divisions of large companies are also associates. Members operate within various industrial sectors applying biotech developments, such as: pharmaceutical laboratories, diagnostic laboratories, agri-foodstuffs, fine chemicals, energy, the environment, the process industry and equipment sectors.

Amongst the main activities and services offered by ASSOBIOTEC, most noteworthy is its support for biotechnological development in both Italy and the EU and it is a point of reference for Italian companies involved in the production and marketing of products derived from both the traditional and innovative applications of biotechnology.

4.5. BIOTECHNOLOGY IN TURKEY

4.5.1. TÜBITAK

The Scientific and Technical Research Council of Turkey (TÜBITAK)[24], created in 1963, is the leading body in Turkey responsible for the promotion, development, organisation and co-ordination of research and development in scientific areas. TÜBITAK operates under the Turkish Government's national objectives for economic development and technological progress. The main duties of TÜBITAK are:

- To apply the Turkish Government's policy on science and technology.
- To co-ordinate, commission and support scientific research.
- To create and sustain specialised institutes to undertake Research and Development projects. The objectives are laid out in five-year plans and consider economic developments and the priorities established by the Council itself.
- To support research through grants and other means. Furthermore, special emphasis is given to the recruitment and training of future scientists.
- To support R&D projects and innovation in industry, and to encourage collaboration between industry and university by building technological parks in order to facilitate these objectives.
- To implement scientific projects in an international arena under scientific and technical accords.
- To facilitate public access to scientific information published in scientific magazines, books and journals.
- To support scientists and researchers through awards and encouraging the publication of scientific work.

An important part of TÜBITAK's central administrative apparatus is the Research Grant Committee. This Committee helps optimise the help given by the Council to R&D projects. One of the main tasks is project evaluation and the designation of winning projects in the following areas:

[23] Web site: http://www.assobiotec.it
[24] Web site: http://www.tubitak.gov.tr/english/

- Pure science,
- Electricity, electronics and IT,
- Mechanical engineering, chemical technology, materials science and manufacturing systems,
- Construction and environmental technology,
- Marine, earth and environmental sciences,
- Health sciences,
- Agricultural, forestry and nutrition technology,
- Veterinarian and livestock sciences.

There are also interdisciplinary centres in universities and public or private institutions, which are subsidised by TÜBITAK. In these centres, Research and Development productivity is promoted, scientific and technical projects are generated, and they generate knowledge and offer solutions to problems or research objectives. They likewise act as training centres for new researchers. These centres are the TÜBITAK Research Units, which depend on the Research Committee, and are listed below:

- Astrophysics Research Unit (TBAG),
- Biodiversity Information Research Unit (TBAG),
- Environmental Biotechnology Research Unit (YDABAG),
- Experimental Surgery Research Unit (SBAG),
- Global Tectonics Research Unit (MISAG),
- Hereditary Immunodeficiency Unit (SBAG),
- Housing Research Unit (INTAG),
- Polymer Biomaterial Science and Technology Research and Application Unit (TBAG),
- Basic Neurosciences Unit (SBAG).

Industrial Development Programmes

El TÜBITAK is particularly interested in developing R&D industrial development projects through three programmes or centres:

- **Technology Monitoring and Evaluation Board (TIDEB):** The TIDEB monitors established industrial research projects. These projects fall within the framework of new products, production methods and technological innovation. Care is taken that these projects are carried out in compliance with international standards and standard R&D research practices. Furthermore, TIDEB allows for the planning of studies to improve technological development and to establish policies to increase co-operation between university and industry.
- **The University-Industry Joint Research Centres Programme (ÜSAMP):** The University-Industry Joint Research Centres Programme was set up in September 1996 to develop close links between industry and university departments in order to bring about technologically creative fundamental and applied research.
- **TÜBITAK Marmara Research Centre Technological Free Zone:** In 1999 a technological free zone was established by the Marmara Research Centre to carry out R&D projects with Industry. This is the only example of a science park combined with a free zone in Turkey.

Marmara Research Centre (MRC)

The TÜBITAK Marmara Research Centre, (MRC) was founded in 1972, in Gebze, Izmit. This Centre is responsible (under a strategic quality plan) for carrying out applied scientific research aimed at industry, and for proposing projects for industrial development stemming from theoretical research.

The Centre includes the following institutes and research laboratories:

- Information Technologies Research Centre (BTAE/ITRI),
- Energy Systems and Environmental Impacts Research Institute (ESCAE/ESERI),
- Genetic Engineering and Biotechnology Research Institute (GMBAE/RIGEB),
- Food Science and Technology Research Institute (GBTAE/FSTRI) (GBTAE/FSTRI),
- Food Analysis Laboratory,
- Materials and Chemical Technologies Research Institute (MKTAE/MCTRI),
- Earth and Marine Sciences Research Institute (YBAE/EMSRI),
- Technological Free Zone,
- International Centre for High Technologies, Science, Education and Training (ICHTS),
- Turkish-Ukrainian Joint Research Laboratory (TUJRL).

The Marmara Research Centre is one of the centres of reference in scientific research and applied industrial technology in Turkey. Its aim is to develop Turkey's competitive potential.

TÜBITAK-MRC Biotechnology projects

The biotechnology projects that have been carried out are mostly carried out at the Food Science and Technology Research Institute (GBTAE/FSTRI). The list of projects is as follows[25]:

- Single cell production from yeast (1980): Aimed at the feed industry.
- Production of some algae species for nutritional purposes (1987): Aimed at the food and feed industry.
- Application of the California Black Olive Production Method to Turkish Olive Variety (KARIN GIDA, 1997).
- Fermentation Technologies in Food Production: Starter Culture Applications to Traditional Turkish Foods (NATO-Science for Stability,1987-1993).
- Production and preservation of Boza, a traditional Turkish drink, (VEFA BOZACISI, 1984).
- Microbial rennin production (1982): Aimed at the dairy industry.
- Production of biodegradable plastics by microorganisms (EUREKA Project, 1999-2001). Aimed at the packaging industry.
- Yoghurt production with starter cultures (TSEK,1985): Aimed at the dairy industry.
- Citric acid production from 7 different *Aspergillus niger* species (1983): Aimed at the food industry.
- Establishment of mould culture collection and detection of characteristics of fungi (1993-1995): Aimed at the food industry.

[25] Contacts: Prof. Güner Özay (Associate Professor) and Dr Mehlika Borcaklı

- Mycotoxins of moulds originating from Turkish foods and decontamination (1979-1985): Aimed at the dairy industry.
- Probiotic and antimicrobial activity detection of lactic acid bacteria originating from curd cheese and olives (2000-2001): Aimed at the food and feed industry.

4.5.2. Bogazici University, Istanbul

Bogazici University, initially founded as Robert College in 1863, was the first American College established outside the United States. As such it has a long academic tradition of high quality education. It is a relatively small school where each student can be given individual attention. Its language of instruction is English, which opens the widest possible window to modern communication for its students. The faculty comprises the best researchers in Turkey, and most of its members have at least one graduate degree from the prominent universities in the United States, England or Canada.

Bogazici University was formally established on September 10, 1971. While thus appearing to be a newcomer to the community of Turkish universities, it has behind it the long history of Robert College, which was the first American College to be established outside the boundaries of the United States. With the transfer of the site to the Turkish government, Bogazici University became the direct heir not only to the excellent facilities of Robert College but also to its distinguished academic tradition.

In 1971, Bogazici University had three faculties plus one school of higher education. Since 1982, it has grown to include four faculties, six institutes (offering graduate programmes), the School of Foreign Languages, the School of Applied Disciplines and the School of Advanced Vocational Studies. The University's four faculties are: Arts and Sciences, Engineering, Economics and Administrative Sciences, and Education. Many members of staff teach in more than one faculty and the faculty structure promotes interdisciplinary teaching whenever appropriate.

Many of the University's buildings are located on its South Campus, with the Bosphorus and the historical castle of Rumelihisar as its boundary to the east. This campus encompasses the oldest buildings of the University. The North Campus and the Hisar Campus contain the newer additions to the University facilities. A fourth campus, on the Asiatic side of the Bosphorus, houses the historic Kandilli Observatory which is the centre of a nationwide network of seismic stations and a prominent research unit of the University. The fifth campus, the Kilyos (Saritepe) Campus, is situated on the shores of the Black Sea 20 km to the northwest of the South and North campuses.

The School was founded in 1912 as part of Robert College offering the B.S. degree in Civil, Electrical and Mechanical Engineering. In 1958, Department of Chemical Engineering was established and post-graduate programmes, leading to the *MSc* degree in all four fields of study, were started. The School of Engineering of Robert College was transformed into Bogazici University in 1971 together with the School of Sciences and Foreign Languages and the School of Business Administration. Two new departments, Nuclear Engineering and Industrial Engineering were founded in 1973 and doctoral programmes in all six fields of engineering were initiated in the same year. In 1981, the Department of Computer Engineering was added to the roster.

The Faculty of Engineering is composed of six departments that offer four-year programmes leading to the degree of Bachelor of Science as well as graduate degrees both at *MSc* and PhD levels. The departments are listed as:

- Chemical Engineering,
- Civil Engineering,
- Computer Engineering,
- Electrical and Electronics Engineering,
- Industrial Engineering,
- Mechanical Engineering.

Chemical Engineering Department (Faculty of Engineering)

The Chemical Engineering Department's Biochemical Engineering Laboratory, with a team of 4 or 5 professors, focuses on the following areas:

- **Fermentation Technology:** *E. coli, S. cerevisiae, T. aquaticus, P. stuartii, S. coelicolor.*
- **Recombinant DNA Technology:**
  - Modification of microorganisms by genetic engineering,
  - Overexpression and production of recombinant proteins,
  - Extension of the substrate range,
  - Secretion of heterologous proteins,
  - Mutation and SNP detection in the human genome.
- **Downstream Operations:** Purification of restriction enzymes, antibiotics and therapeutic proteins.
- **Metabolic Engineering:**
  - Extension of the substrate range,
  - Metabolic flux analysis of biomass and ethanol production by *Saccharomyces cerevisiae.*
- **Computer Simulation of Fermentation and Downstream Processes by numerical Methods.**

Bogazici University funds the research projects carried out in the Department of Chemical Engineering and other research projects. The following studies have been carried out under the leadership of Kutlu S. Ozergin Ulgen:

- Fermentation Characteristics of *Thermus aquaticus* and the Purification of its Enzyme TaqI (1995-1996).
- Estimation of Biomass and Product Concentrations from Measured Substrate Concentration via Asymptotic Observer (1995-1996).
- Optimisation of Operating Parameters for Protein Purification with Chromatographic Columns (1996-1997).
- Fuzzy Modelling and Control of a Biological Process (1997-1999).
- Modelling of the Purification of TaqI Endonuclease by Linear Gradient Elution Ion Exchange Chromatography (1997 –1999).
- Modelling and Experimental Studies of Protein Purification in an Expanded Bed Adsorption Chromatography (1998-1999).
- A Study of Protein and DNA Analysis by Capillary Electrophoresis (1998-1999).

- Development of Expanded Bed Technique for Purification of Actinorhodin from *Streptomyces coelicolor* A3(2) (1998-1999).
- Purification of PstI Endonuclease from Providencia Stuartii 164 (1999-2001).
- Purification of Therapeutic Recombinant Proteins of Human Origin (2000-2001).
- Production of CFTR protein for Gene Therapy (2001-).
- Bioprocess Design of a Therapeutic Protein (2001-2002).
- Metabolic Engineering (2002-).
- Bioreactor Operating Strategies for Alcohol Fermentation by Recombinant Yeast (1999-2001).
- Modelling of enzyme reproduction restriction by recombinant *E. coli* (2000-2001).

The following research projects have also been carried out with the support of Bogazici University:

- Fermentation characterisation determination for *Thermus aquaticus* (Project code: 96A0519)
- Purification of restriction enzymes by high pressure liquid chromatography (Project code: 97HA0501)
- Purification of proteins by fluidised bed chromatography (Project code: 98HA501)
- Analytical Methods developed for proteins by Capillary Electrophoresis (Project code: 99HA502D)
- Bioreactor Operating Strategies for Alcohol Fermentation by Recombinant Yeast (Project code: 00A502).

Institute of Environmental Sciences

The Institute of Environmental Sciences was founded in 1983 as an extension and restructuring of the Environmental Research Group established in the School of Engineering during the late 1970s. Starting with three graduate students in the fall semester of the 1984/1985 academic year, the Institute had its first graduates in 1986, and since then 121 *MSc* and 21 PhD degrees were awarded in the fields of Environmental Sciences and Environmental Technology. The Institute's academic staff consists of 17 research assistants and 5 expert technical personnel. The 2001/2002 academic year had 29 PhD. and 89 *MSc*. students working towards degrees. The goals of the programmes are to prepare professional environmental scientists, engineers and researchers, who can deal with the complexities of environmental problems, propose scientifically and economically meaningful solutions, develop recommendations for sound policies and devise means to implement the policies adopted.

Furthermore, the Institute aims to emphasize the importance of appropriate environmental technologies, and act as a leading institution for developing countries. Apart from teaching and research, the Institute offers consultancy services on the environmental problems faced by industry.

The Institute of Environmental Sciences offers several MSc and PhD degrees. In the *MSc* programmes the following degrees are given:

- Students with engineering background receive an M.Sc in Engineering upon completion of the *MSc programme in Environmental Technology;*

- Students with engineering or pure sciences or social sciences background receive an *MSc in Environmental Sciences-Pure Science* or an *MSc in Social Environmental Sciences* upon completion of the appropriate MSc programme in Environmental Sciences;
- Students with a pure sciences background receive an *MSc* in Environmental Technology upon completion of the *MSc* programme in Environmental Technology.

Students with a degree from any branch of Engineering, Pure Sciences, Social Sciences, Economics, Political and Administrative Sciences may apply for the *MSc* programmes. The *MSc* programmes require at least 27 credit hours of course work and a written thesis. Civil, Mechanical, Electrical and Electronics, Computer, Engineering graduates applying to the Environmental Technology programme may have to take preparatory courses before they start the formal courses of the programme. Environmental and Chemical Engineering graduates are not required to take preparatory courses for the Environmental Technology programme. There are no preparatory courses for the Environmental Sciences programme. The duration of the MSc programmes is normally 2 years.

The goal of the Institute of Environmental Sciences is to prepare professional environmental scientists, engineers and researches, who can deal with the complexities of environmental problems, propose scientifically and economically meaningful solutions, develop recommendations for sound policies adopted. Furthermore, the institute aims to emphasize the importance of appropriate environmental technologies, intending to act as a leader institution for developing countries. Apart from teaching and research, the Institute offers consultancy services on the environmental problems faced by the industry. Current topics of interest and expertise are:

- Water and Wastewater Analysis,
- Microbial Analysis,
- Environmental Management Systems (EIA, CP, LCA, ISO 14001)
- Air Pollution Analysis,
- Solid Waste and Sludge Analysis,
- Determination of Noise Pollution.

The main field of interest of the biotechnological studies carried out in this institute is environmental biotechnology. Key words involved in this discipline include: biofilm, biofilm kinetics, nitrification, denitrification, activated sludge kinetics, inhibition, domestic and industrial wastewater treatment, organochlorine compounds, combined adsorption and biodegradation.

Projects carried out in the department under the leadership of Prof. Dr. Ferhan CECEN:

- 91 HY 0024 (March 1991-March 1993): Treatability of pulp and paper bleaching wastewaters, supported by BU (Keywords: pulp and paper, bleaching wastewater, activated sludge, adsorption, kinetics, isotherms, bioenhancement).
- 93 HY 0028 (October 1992-September 1996): Nitrogen removal from industrial wastewaters by biological treatment, supported by TÜBITAK and BU. (Keywords: fertilizer wastewater, ammonia removal, activated sludge, submerged biofilm filter, kinetics, inhibition).
- 95 Y 0044 (April 1995-July 1997): Application of biological treatment and TiO_2 photocatalyzed oxidation to pulp bleaching wastewaters, supported by BU. (Keywords: pulp and paper bleaching wastewater, activated sludge, photocatalysis, non-biodegradable substances, BOD enhancement).

- 96 HY 0029 (January 1997-June 1998): Investigation of treatability and characterization of landfill leachates. supported by BU. (Keywords: landfill leachates, combined leachate and domestic wastewater treatment, activated sludge, biokinetics, organic carbon removal, nitrification, non-biodegradable matter, heavy metal removal, biosorption of heavy metals).
- 98 HY 02 (August 1998-January 2000): Application of respirometric methods in the biological treatment of landfill leachates with PAC addition. supported by BU. (Keywords: landfill leachate, combined treatment, activated sludge, PAC addition, adsorption, respirometry, inhibition).
- 00 Y 103 (February 2000-January 2002): Assessment of inhibition in the biological treatment of industrial wastewaters supported by BU. (Keywords: industrial wastewater, pharmaceutical wastewater, chemical synthesis, activated sludge, activated carbon, adsorption).
- BAP-02Y101D (from March 2002): Cometabolic removal of chlorinated organics in nitrifying systems (supported by BU and TÜBITAK). (Keywords: cometabolism, chlorinated organics, nitrifcation, biofilm reactor, activated sludge).
- BAP-02Y102 (from March 2002): Combination of activated carbon adsorption with biological processes for the removal of slowly biodegradable and toxic compounds supported by BU. (Keywords: aromatic compounds, chlorinated aromatics, activated sludge, adsorption bioregeneration).
- Agricultural Pesticides Inc. (1987-1988): Wastewater treatment plant design for domestic, salty and acidic-alkaline wastewaters of a pesticides manufacturing company.
- Lever-Iş Cleaning Agents Inc. (1988): Wastewater treatment plant design for a detergents manufacturing company.

4.5.3. Bioglobal Agricultural Production and Consultancy

Bioglobal Agricultural Production and Consultancy was created in the year 2000[26]. They work mainly with:

- biological pesticides,
- organic soil improvers,
- seed.

The work the company is involved in can be classified as follows:

1. Providing agricultural income from natural and international sources;
2. Market analyses, evaluation and coordination of agricultural investments, its marketing and project development;
3. Appropriate input realization, patent works:
4. Consultancy for the international companies on their interest in Turkey.

Bioglobal Agricultural Production and Consultancy are also the representatives of the Australian company Bio-Care and offer consultancy services to Italian, Spanish and Belgian companies, along with three national firms, on planting and seed investment and marketing.

[26] Contact: Özgür Ateş.

The R&D projects carried out seek environmental protection through avoiding the use of persistent toxic chemicals in agriculture and developing biological pesticides.

4.5.4. Istanbul Technical University (ITU), Istanbul

The ITU was established in 1773. The university had many responsibilities for the innovation actions of Ottoman Empire. During the first period of the Republic of Turkey, ITU played an important role in the construction of dams, bridges, highways, industrial plants and power plants.

The main campus is the Ayazaga campus, which is the site of the faculties of Civil Engineering, Marine Engineering, Aeronautical Engineering, Chemical-Metallurgical Engineering, Mining Engineering, Electrical-Electronic Engineering and the research institutes of Asia, Europe, Earth Sciences, Nuclear Energy and Information Technologies. There are also 4 other campuses where architecture, mechanical engineering faculties are established.

Biotechnology classes are given in the Chemical and Metallurgical Engineering Faculty. This faculty has Chemical, Metallurgical and Food Engineering departments.

The Chemical and Metallurgical Engineering Faculty dates back to 1958, when the Chemical Engineering Department in The Technical School (Teknik Okul) of ITU was established. This Department had a four-year B.Sc. equivalent course, which was oriented more towards chemical technology.

The Metallurgical Engineering branch of the faculty was started as a department in the Mining Faculty in 1961.

In 1963, the Chemistry Faculty offered a five-year engineering programme, somewhat equivalent to an M.Sc. In 1971, together with all other faculties, both Chemical and Mining Faculties accepted the B.Sc. and *M.Sc.* concepts as practiced in the Anglo-Saxon world involving 4 and 2 years respectively. The Metallurgical Engineering Department was expanded into the Metallurgy Faculty in 1978.

In 1982, the Chemistry Faculty was split into two Departments: the Department of Chemical Engineering and the Department of Chemistry. The former merged with the Metallurgical Engineering Department thus creating the Faculty of Chemical and Metallurgical Engineering. Later, due to the Department's specialisation, trends on a world scale and at some Turkish universities, in 1998, the name of the Department of Metallurgical Engineering was changed to the Department of Metallurgical and Materials Engineering. As for the Department of Chemistry and the Mathematics, Physics and Engineering Departments became the Faculty of Arts and Sciences.

On the other hand, in 1990 the Department of Food engineering was set up, which was the first in the Mármara region, in response to the demand made by the region's food sector.

In this chapter we concentrate on the activities of the Department of Chemical engineering and the Department of Food Engineering.

Chemical Engineering Department (Faculty of Chemical and Metallurgical Engineering)

Around 10 professors work on biotechnology in this department under the leadership of: Prof. Dr. Nuran Deveci, Dr. Moiz Elnekave and Prof.Dr. Ayse Aksoy. The projects carried out on biotechnology are:

- Anaerobic treatment by using bread yeast and its treatment (1998-2001). Financially supported by Istanbul Technical University (ITU).
- Sulphate compound cracking in pulp and paper wastewater (1996). Financially supported by Istanbul Technical University (ITU).
- Sulphur production from phosphochips by microbiological methods (1995). Financially supported by Istanbul Technical University (ITU).
- Purification of acid phosphate enzyme from tomato (2000). Financially supported by Istanbul Technical University (ITU).
- Paracetamol waste water treatment by anaerobic process (1997). Financially supported by Istanbul Technical University (ITU).
- Anaerobic treatment of antibiotic wastewater (1997-2001). Financially supported by Istanbul Technical University (ITU).
- Investigation of Enantioselectivity of *Nigella sativa L.* Seed Lipase
  Co-operation between: CNR and ITU). Sponsored by CNR (Consiglio Nazionale delle Ricerche) / TÜBITAK.

Food engineering department (Faculty of Chemical and Metallurgical Engineering)

The Food Engineering department, currently directed by Prof. Necla Aran, was established in 1990 with 30 students per year. The department then started to offer *MSc* programmes in 1992 and PhD programmes in 1995.

The Food Engineering Department is carrying out projects for Government Bodies and private companies on production, quality control, marketing and quality insurance. The biotechnology studies carried out are summarized below:

- Fermentation Technologies in Food Production (NATO Science for Stability) (Araştirici). Financially supported by: TÜBITAK-NATO.
- The appropriate production of yeast in molasses for use as food for birds. Financially supported by TÜBITAK-Private company.
- Biomass production (rich in protein) from agricultural wastes. Financially Supported by TÜBITAK and Yem Industry Ltd.
- Citric acid production. Financially Supported by TÜBITAK and the Private sector.
- Biomass production (rich in oil) from agricultural wastes. Financially Supported by TÜBITAK.
- Protein production from vegetable waters from the olive oil industry and cheese whey. Financially Supported by TÜBITAK.
- Protein production from dry grape pomace from the vinification process. Financially Supported by TÜBITAK.

4.5.5. Ege University, Izmir

Ege University, located in Izmir, was founded in 1955 and is one of the largest universities in Turkey. It consists of 11 faculties; including engineering, medicine, social sciences, art, education, science, history, 7 research institutes, 21 R&D centres, 13 advanced schools. The university has the number of 30,000 students for education and 2,809 academicians.

The Faculty of Engineering of Ege University was the first in Turkey to offer a Biotechnology Engineering degree. The many advances that have taken place in the spheres of biochemistry, microbiology, molecular biology, cell metabolism, engineering and material sciences have enabled biological developments to become integrated with engineering principles for living organisms and solutions found for the problems they face.

The department itself deals with the following topics: Mass and heat transfer, kinetics, biocatalyst, biomechanics, separation and purification techniques, bioreactor design, surface science, fluid mechanics, thermodynamics and polymer chemistry of engineering topics. Genetics, molecular biology, protein chemistry, metabolism, bioelectrics, immunology, pharmacology topics of pure and applied science.

Considering the research areas mentioned above, the department deals with both research and development projects and also applied industrial projects. The department itself acts as a bridge between industry and R&D.

Biotechnological industrial developments and their application are of great importance within the framework of the department's goals.

The industrial applications of the department consist of:

- Food,
- Renewable energy sources (hydrogen, ethanol, biogas),
- Medicines (antibiotics, vitamins, hormones),
- Inoculation,
- Biochemical materials (proteins, amino acids, enzymes, organic acid, pesticides, various polymers),
- Biomedical systems,
- Transgenic plants, and animal types,
- Mining, wastewater treatment, industrial waste treatment.

The department has a staff of 12 and 30 students under the leadership of Prof. Fazilet Vardar Sukan.

Below is a list of projects carried out in the Biotechnology Engineering Department of the Engineering Faculty of Ege University:

- The Isolation, Identification, Molecular Biology and Applications of Thermophilic Bacteria from Hot Springs in Turkey (2000-2004). Cooperation with Biotechnology Eng. of Ege University and Queen Mary & Westfield College. Financially Supported by British Council, EBILTEM.

- Conservation of Various Types of Olives in Glass Containers without brine Process Application (2001-2003). Cooperation among: Olive Research Institute and the Biotechnology and Food depts. of Ege University. Financially supported by: TAGEM.
- *Yersinia Enterocolitica* and *Aeromonas Hydrophila* and Microbiologial Observation for Izmir Domestic Water (2001-2004). Cooperation among: the Centre for Env. Application and Research of environmental problems of Ege University, Bioeng. Dept and Biology dept. of Ege University. Supported by Ege University. and Izmir Water & Sewage systems.
- Observation of ochratoxin-A Production in Figs (2001-2003). Cooperation among: the Bio-engineering, Biology and agricultural Engineering Departments. of Ege University. TARIŞ Inc, Ege Dry fruıt association. Financially supported by TÜBITAK.
- Research on the Production of Commercially Important Plants through Tissue Culture Techniques (2001-2003). Co-operation between the Biotechnology Dept and the Agriculture Faculty of Ege University. Financilally supported by: EBILTEM.
- A Study on *Agarigus Bisphorus* mushrooms by Rapid Markers (2001-2004). Cooperation between: Biotechnology Eng. Dept. of Ege University, Agriculture Faculty of Ege University. Financially supported by Ege University.
- Investigation of the Effects of the *Spirulina platensis* Extracts (Crude Extract, *Ca-Spirulan* and *Phycocyanin)* on Tumour Cell-Lines (2001-2004). Co-operation between: the Bio-technology Engineering Dept. and the Molecular Biology section of the Biology Dept. of Ege University. Financially supported by; DPT (governmental planning organisation and EBILTEM.
- Large-Scale Production of a combination of biopreparations Bio Combination that can be used in Agricultural Biological Warfare (2002-2003). Co-operation between the Child Health section of the Faculty of Medicine and the Biotechnology Dept of Ege University. Financially supported by: Ege University.
- Mechanism and Kinetics of Treatment of Phenolic Compounds in Vegetable Waters from Olive Oil Production by Natural Adsorbants (2002-2003). Financially supported by Ege University.
- Mediterranean Usage of Biotechnologically Treated Effluent Water (Medusa Water Project) (1999-2003). Co-operatıon among: Portugal, Italy, Spain, Morocco, Tunisia, Turkey. Financially suppor-ted by EU and EBILTEM.
- Cloning of the DNA marker that controls *Ascochyta rabiei* strength in *Cicer arietinum* L. and its mapping in *Cicer Arietinum* L. (2000-2004). Financially supported by DPT (Government Planning Organisation).
- Reddening of Cotton *(Gossypium hirsutum* L.) Leaves: Causes and Biochemical Mechanism (2000-2003). Co-operation among: the Dept. of Biotechnology Engineering of Ege University, the Agriculture faculty of Ege University, and the Bulgarian Academy of Sciences. Financially supported by: Bulgarian Academy of Sciences, TÜBITAK, ITAŞ TEKNOPART INC, TARIS INC.
- Production of naturally-dyed organic cotton (2000-2002). Co-operation between: the Dept. of Biotechnology Engineering and the, Agriculture Faculty of Ege University. Financially supported by: RAPUNZEL Inc and Izmir-ITAŞ TEKNOPARK Inc.

- Appropriate naturally -dyed Cotton Production in The Eagean Region (2000-2002). Co-operation between: the Dept. of Biotechnology Engineering and the Agriculture Faculty of Ege University. Financially supported by Izmir-ITAŞTEKNOPARK Inc.
- Synthetic Peptide Vaccination Preparation together with new antigen conjugates which can be used as Immunogen and Adjuvant (1998-2002). Co-operation among: the Dept. of Biotechnology Engineering of Ege University, TÜBITAK-MRC Gebze. Financially supported by TAGEM, EBILTEM, TÜBITAK.
- Activity Capacity Determination for the Various Extracts of *Spirulina Platensis* which are Produced in Turkey. Co-operation among: Biotechnology Eng. Dept. of Ege University, Biology Dept of Ege University, Nuclear Medicine Section of Medicine Faculty of Ege University, Water Products Institute of Ege University. Financially supported by: Industry and EBILTEM.
- Investigation of Ochratoxin Production in Grapes and Identification with Isolation of Potential Mould Formation (1999-2002). Co-operation among Biotechnology Eng of Ege University, Agriculture Faculty of Ege University, R&D Dept of Taris Inc. Financially supported by: DPT.
- Culture Collection of Microalgae from Inner Waters (2001-2003). Financially supported by TÜBITAK and EBILTEM.
- Radioprotective Impacts of Spirulina Alginin on the Immune System using them as Experimental Animals (2000-2002). Co-operation among Nuclear Medicine Section of Ege University. Medicine Faculty, Izmır Ataturk Research Hospital, Biotechnology Eng. Department of Ege University, Onkomer Inc. Financially supported by: EBILTEM and Industry.
- Establishment of an Action Plan for Sustainable Development for Yuvarlak Cay (Koycegiz-Dalyan Special Environmental Protection Area) (2000-2002). Co-operation among: Biotechnology dept of Ege University, Water products Faculty of Ege University, Industrial Microbiology Section of Biology Dept of Ege University. Financially supported by: Ministry of Environment of Turkish Republic.
- Gelatine Wound Cover Production and Characterisation (2000-2003). Co-operation among: Biotechnology Eng. Dept. of Ege university and Chemical Eng. Dept. of Hacettepe university. Financially supported by Hacettepe University.
- Monoclonal antibody Production in Polyester Fibre Reactors (1998-2002). Co-operation among Biotechnology Eng. Dept. of Ege University and Chemical Eng. Dept. of Hacettepe University. Financially supported by Hacettepe University.
- Lactase with Microbial Source Production from the Vegetable Waters of the Olive Oil Industry (1999-2003). Co-operation among: Biotechnology Eng. and Food Eng. Depts of Ege University. Financially supported by TÜBITAK and EBILTEM.
- *Agaricus bisporus* (Lge) Sing. Production and its genetic analysis (1998-2001). Co-operation among: biotechnology eng., agriculture department. Financially supported by Ege University.

4.5.6. Middle East Technical University, (Ankara)

Founded in 1956, METU is a state University with a twofold objective: training Turkish and foreign students in scientific, technical and professional fields of study, and utilizing these studies in the field of pure and applied research to contribute to the economic and social needs of Turkey and other developing countries. Since its inception the language of instruction has been English.

The Middle East Technical University is devoted to the pursuit and application of knowledge for the social, cultural, economic, scientific and technological development of our society and mankind through achievements in teaching, research and community service that meet the highest international standards.

METU has 39 undergraduate programmes carried out by 37 departments in 5 faculties. Additionally, there are 4 Graduate Schools with 59 programmes and a "School of Foreign Languages" which includes the English Preparatory Department.

Environmental Engineering Department (around 20 academics) is located in Faculty of Engineering (250 academics). The Biotechnology Studies/projects are carried out by permanent 2-3 academic group in the department.

The Biotechnology Projects in The Department of Environmental Engineering, Middle East Technical University. Team Leader: Prof. Dr Celal F. Gökçay. Relevant Applied Research Projects on Biotechnology:

- Recycling of pyritic fly ash by using microbiological techniques-1981. National Scientific Technical Council of Turkey (TÜBITAK) - (Project number: MAG-539).
- Biological Treatment of IMEKS-Abattoir Waste Waters. (Supported by IMEX).
- Treatment of MKE-Elmadag Ammunition Factory Effluents. (Supported by MKE).
- Treatment of Pulp and Paper Industry Waste Waters from SEKA Taskopru Plant. (Supported by SEKA - Turkish State Pulp and Paper Enterprise-Taskopru plant).
- Characterization and Treatability of Chlorinated and Coloured Effluents from SEKA Pulping Plants. (Supported by Directorate General of SEKA (-Turkish State Pulp and Paper Enterprise) - 1993-1995.
- Treatment of Chlorinated Effluents. National Scientific Technical Council of Turkey (TÜBITAK Project number KTCAG-128 1993-1995).

Relevant M.Sc Theses Conducted:

- Bacterial leaching of copper floatation tailings.
- Studies on calcined pyritic fly-ash using microbiological leaching techniques.
- Anaerobic biological treatment of high-strength wastes.
- Characterization of Chlorine Dioxide Bleached Pulp Effluents.
- Physical-Chemical Treatment of Bleaching Process Effluents from SEKA Kastamonu Pulp and Paper Plant.
- Biochemistry of Chlorolignin and Chloropesticide Degradation.
- Assessment of Toxicity and Biodegradability of Pulping Effluents in the Microbial Treatment Community by Electrolytic Respirometry (Pervin Katmer).
- Biological Colour Treatment of Pulp and Paper Industry Effluents.
- Activated Sludge Treatment of AOX from Pulping Wastes.
- Treatment of Chlorinated Compounds by Activated Sludge and Process Microbiology.

4.6. BIOTECHNOLOGY IN ISRAEL[27]

The State body in Israel responsible for managing the development of Biotechnology is the Ministry of Science, Culture and Sport (MOS). Here they hope that the 21st Century will be the century of "Science and Technology". Many resources are to be invested in research and development technology and it is expected that this will be followed by economic growth, social prosperity and the capacity to compete in the world market. It is hoped that the name of Israel will be respected as a consequence of its magnificent achievements in the field of science. This Ministry supports the development of scientific infrastructure, co-operation in international scientific projects and encourages investment in research and development in Israel.

The MOS is responsible for linking fundamental scientific research in Universities with the product-oriented R&D of Israel's industries. The MOS supports leading scientific research and technological infrastructure, international co-operation and the recruitment of scientists. In this way the MOS hopes to contribute to the future of Israel as an international centre for science-related products and services.

The impact of the MOS on the scientific infrastructure in Israel derives from its role of focal point, co-ordinator and representative on a national level. It frequently takes the leading role in identifying, organising and promoting new scientific initiatives in areas of national priority. For example, in 1989, the MOS and the MIT (Ministry of Industry & Trade) together established the National Committee for Biotechnology (NCB) and a high-level committee (the Katzir Committee) responsible for designing a national strategy for successful biotechnological development.

The Katzir Committee's "Report on Biotechnology" (1989) provided detailed, integrated plans to promote Israeli biotechnology. Recently the MOS established a high-level "think-tank" to support the promotion of the use of biotechnological know-how by industry in Israel.

The MOS often works as an important complement to other government departments on initiatives relating to the scientific area. In international affairs for example, the MOS works closely with the Ministry of Foreign Affairs to establish important scientific co-operation agreements with Russia, China, India and many other countries (there are more than 40 countries with which it has agreements of this type).

Other activities of the MOS are of a more domestic nature, for example, together with the Ministry of Agriculture, it supports a national gene bank. The MOS also plays an active role in improving the geographic distribution of R&D opportunities throughout Israel; it has achieved this by helping the regional R&D centres and by creating a Permanent Council for Regional R&D.

Finally, great importance is given to encouraging the public to be aware of and take an interest in scientific matters. For this reason, the MOS informs the public of its activities by free-of-charge publications, and it also maintains an Internet web site from where it replies to public queries and concerns.

[27] Web site: http://www.most.gov.il

4.6.1. Development of Strategic Research

Strategic Research was defined by the Ministry of Science, Culture and Sport as research characterised by its application and economic potential to achieve two goals, namely:

- The exploitation of the latent potential of scientific research to stimulate new generations of high-tech products, which in turn will enable other industrial sectors to compete in a world market;
- To reduce the gap, or build a bridge between basic research and applied research, while lowering the time required for the maturation of practical ideas.

Israel's Strategic Research plan contains the following programmes:

- Advanced Materials and Chemical Technology,
- Biotechnology,
- Electro-optics and Microelectronics,
- Environment and Water Quality,
- Information Technology and Telecommunications,
- Bio-microelectronics,
- Strategic Reserves (Resources),
- Applied Mathematics,
- Internet Infrastructure (Internet2),
- Social Sciences.

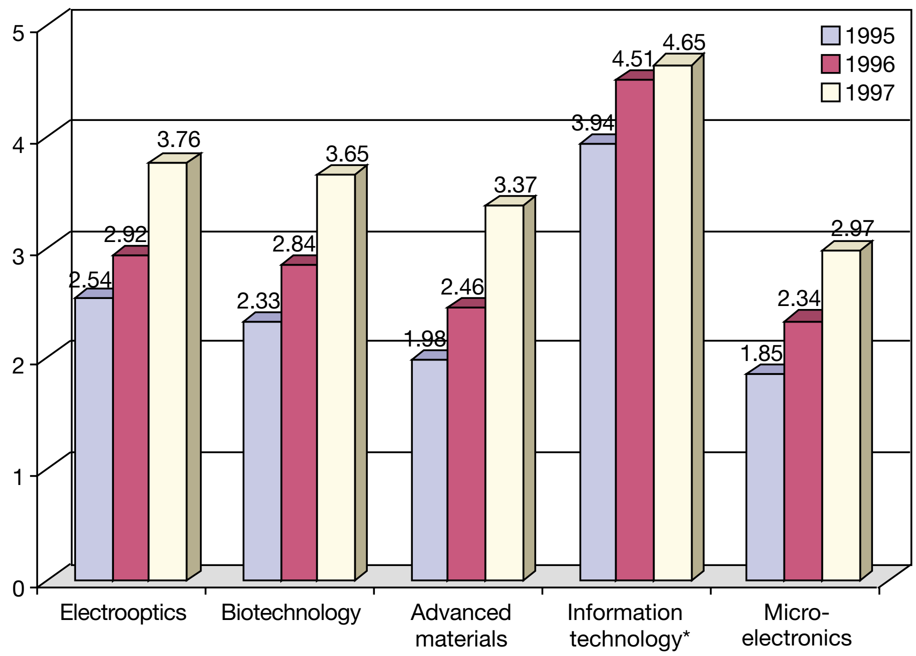
The following principles apply to the Strategic Research development programme:

- Multi-year programme: the ability to envisage the economy's requirements in the area of technology in both the medium and the long term.
- Professional capability: establishment of priorities bearing in mind the diverse technological areas subject to national priorities, including the development of human potential and the development of the scientific equipment infrastructure in accordance with defined criteria.
- The definition of criteria for identifying economic, scientific and socially preferred technological research areas.
- An independent, financial, multi-year framework, of significant volume, for strategic research, structured in such a way that a critical mass is achieved in selected, preferred areas.
- The establishment of cooperation between researchers from different bodies, including researchers from industry itself.

The National Executive Committee for Strategic Scientific Development and Technological Research (also known as the "Committee of Thirteen") was appointed in January 1994 by the Ministerial Committee for Science and Technology. Its mission was to encourage strategic research. At the same time committees were formed on a national scale for the different priority areas that had been established. The Committee of Thirteen and the national committees assisted the Ministry of Science in identifying the areas where Israel held a position of advantage, and to focus its efforts on developing new technologies in order to improve existing ones. It is very likely that these projects will be commissioned, as the economics makes them compatible with Israel's industrial capabilities.

The aim of the programme is to develop scientific and technological infrastructure, bearing in mind the economic requirements on a medium to long- term basis, in order to stimulate the latent economic potential within scientific-technical knowledge and improve the already marked growth rate of the national economy. Within the framework laid down from 1995-1996, the Ministry supports the research programme with more than 26 million euros. This covers research projects, human resource training of scientists, purchase of specific research equipment, the establishment of the Inter-university Centre for Super-computing and the restoration of the Micro-electronics Centre at the Technion-Israel Institute which was damaged by fire.

Figure 10
BUDGET EVOLUTION FROM 1995 TO 1997 IN THE FIVE AREAS OF GREATEST STRATEGIC PRIORITY
In millions of euros (1997 rate)

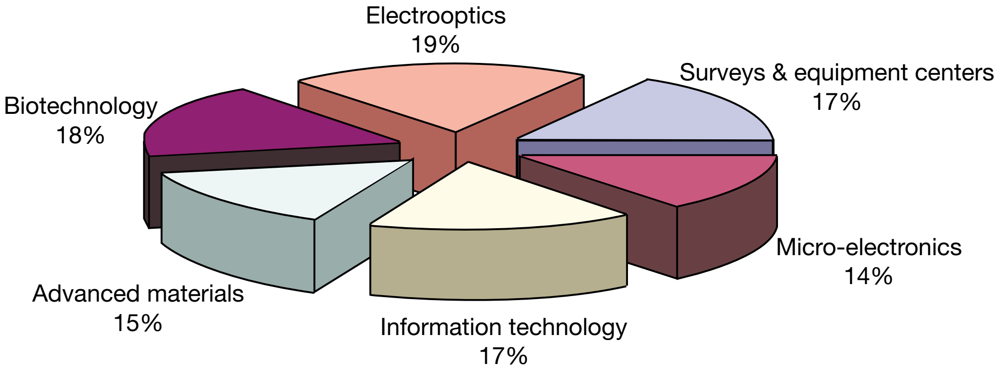


* Includes the creation of the Super-computing Centre

During the years 1995-96, within the Strategic Research Programme, calls for proposals were issued in six priority areas: Electrooptics, Information Technology, Advanced Materials, Microelectronics, Biotechnology and Applied Mathematics. In response, 405 projects were presented by various research bodies in Israel, involving 1,400 consolidated research groups.

Following the recommendations made by evaluators, 110 research projects were financed in 1995 and 1996, and 54 grants were awarded in the six areas of priority stipulated in the tender. The sums allocated totalled 8.90 million euros in 1995 and 14.11 million euros in 1996.

Figure11
1995 BUDGET OF THE INFRASTRUCTURE PROGRAM (IMPLEMENTED)

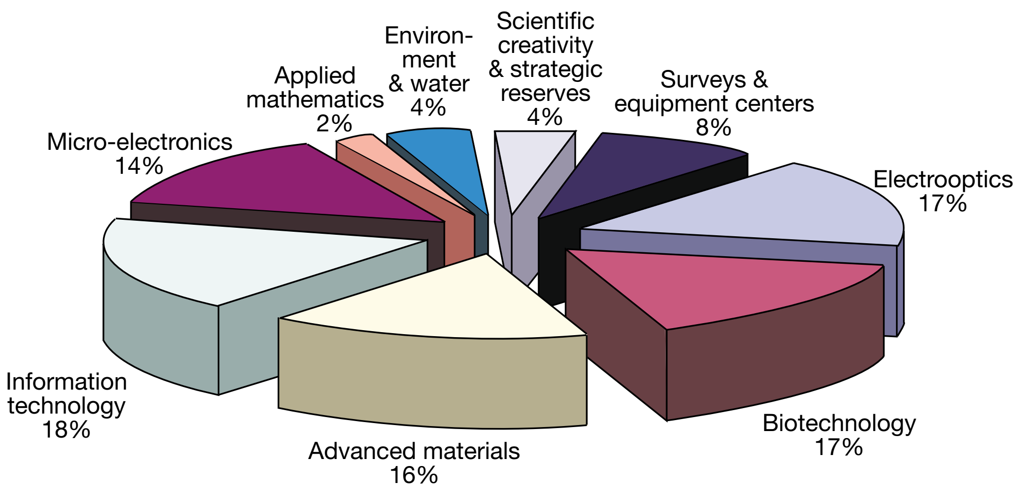


The 1997 financing of the strategic research programme aimed to bring about research in the following categories:

- Extension of Research Projects: continuance of the finance of research projects begun in 1995 and 1996. This activity was originally contemplated.
- Expansion: the financing of new research projects defined within the sub-categories of the 6 areas defined as priorities in previous years.
- Augmentation: adding new sub-categories to the 6 national priority areas.
- New Research area: promoting new research activities in areas essential to strategic research related to environmental problems and to water supply.

Furthermore, in 1997, the Ministry made a call for tender for research projects in 7 areas: Electrooptics, Biotechnology, Advanced Materials, Information Technology, Micro-electronics, and Applied and Industrial Mathematics and, finally, topics related to the new priority area of Environmental Research, including the development and control of Water Supply.

Figure 12
1997 BUDGET OF THE INFRASTRUCTURE PROGRAM (PLANNED)



4.6.2. The Israeli National Biotechnology Steering Committee

The Israeli National Biotechnology Steering Committee began its presentation with a quote from Chaim Weizmann, (1946):

> "I feel sure that Science will bring to his land both peace and a renewal of its yout, creating here the springs of a new spiritual and material life. And here I speak of science for its own sake, and for applied science".

The Israeli National Committee for Biotechnology Management acts as an advisory body and is formed by outstanding industrial and academic experts in the field of biotechnology. The mission of the Committee is to advise the Government on national policy relating to biotechnology, including negotiating investment in biotechnology industries, the support for scientific research activities with applied project initiatives, the withstanding of the critical period between academic research and business involvement in projects, and to facilitate international collaboration.

4.6.3. National Biotechnology Centres

The National Biotechnology Centres were established by the Committee and the Ministry of Science. These are intermediate strategic research centres, needing advanced instrumentation, and collaborative projects. The National Centres are:

- Bioinformatic-genetic infrastructure,
- Protein Purification and Sequencing Technologies,
- Plant Genome Center,
- Gene-Targeted Animals,
- Genome Technologies,
- *High-Throughput Screening.*

4.6.4. Biotechnology Companies

Biotechnology companies are grouped into the following categories:

- Therapeutics,
- Diagnostics,
- Ag-Bio,
- Platform Technologies,
- Academic R&D,
- Cosmetics,
- Bio Nutraceuticals,
- Services, Contract Research and Manufacturing.

Table 4 shows the number of biotechnology companies, sector sales and the number of employees for the period 1988-1998.

Table 4: Biotechnology companies, sales and number of employees

	1988	1990	1992	1993	1995	1997	1998
Sales (million euros)	15.11	50.37	18.34	210.56	251.16	338.51	388.86
Employees	400	600	2,170	2,540	2,835	3,500	3,800
No. of companies	25	30	63	87	100	135	

Below, table 5 groups biotechnology companies by size:

Table 5: Number of biotechnology companies by size

Size of company	Number
Start-Up (Less than 2 years old and <49 employees)	39
Small (<49 employees)	44
Medium (49-50 employees)	11
Large (>150 employees)	7

Table 6 shows the number of companies in each sector by size.

Table 6: Number of companies by size and sector

	Large	Medium	Small	Start up	Total
Therapeutic	3	3	12	18	36
Diagnostic	-	5	12	12	29
Agro-Bio	4	3	21	6	34
Technology Platform	1	4	14	6	25
Environmental	-	-	13	5	18
Cosmetics	1	-	2	8	11
Bio-Nutraceutical	-	-	3	2	5
Services, Research Contracts and Manufacture					11
Other					9

4.6.5. Academic R&D and Research Centres

Among the academic centres and companies devoted to research and R&D we highlight the following:

- B.G. Negev Technologies and Applications Ltd.
- Bar Ilan Research & Development Co. Ltd.
- Dimotech Ltd.
- Hadasit - Medical Research Services & Development Ltd.
- IMI (Tami) Institute Research and Development Ltd.
- Life Science Research Israel Ltd.
- Migal - Galilee Technological Center
- Peri Development Applications (1985) Ltd.
- Ramot - Tel-Aviv University Authority for Applied Research & Industrial Development Ltd.
- Yeda Research & Development Co. Ltd.
- Yissum Research Development Company of the Hebrew University

4.7. BIOTECHNOLOGY IN GREECE

4.7.1. The National Hellenic Research Foundation (NHRF)

The National Hellenic Research Foundation (NHRF) was established by Royal Decree on 9-10-1958 with the aim of the organisation, the financing and the material or moral support of scientific research projects at the highest level. In its 39 years of operation the NHRF has developed scientific and research activity in the areas of historical research, physics, chemistry, material sciences, biology and biotechnology. It has established and organised the largest library of scientific periodicals of all specialisations in the Balkans (about 1,800 titles) and has financed basic research programmes in Institutes of Higher Education, hospitals and the other research organisations in Greece.

The following Research Institutes and other Services comprise the NHRF today[28].

- Byzantine Research (IBR),
- Neohellenic Research (INR),
- Greek & Roman Antiquity (IGRA),
- Biological Research & Biotechnology (IBRB),
- Theoretical & Physical Chemistry (ITPC),
- Organic & Pharmaceutical Chemistry (IOPC).

4.7.2. Institute of Biological Research & Biotechnology (IBRB)

The Institute of Biological Research and Biotechnology (IBRB) was established in 1977 as the third Science Institute of the National Hellenic Research Foundation with the aim of:

- Advancing fundamental research in Basic Biological Sciences and strengthening of the infrastructure in this field,
- Exploiting the results of basic biological and biomedical research for applied research and biotechnology,
- Training of undergraduates, graduates, post-doctoral fellows and technical personnel.

Research activities of the Institute

The Institute's activities in the field of basic research are focused on the regulation of cell metabolism, in health and disease, at the transcriptional, post-transcriptional and post-translational level and on the structure-function relationships of enzyme action. The various research groups developed within this framework, applying biochemical, molecular and cell biological techniques, carry out the following research programmes:

- Molecular Biology,
- Molecular Endocrinology,
- Gene Regulation,
- Chemical Carcinogenesis,
- Cellular Ageing Programme,
- Cellular Function and Regulation-Protein Phosphorylation,
- Regulation of Protein Structure and Function,
- Enzyme Technology,
- Biomimetics.

The various programmes can be grouped in three main research areas:

- Cell and Molecular Biology, Physiology and Pathophysiology,
- Chemical Carcinogenesis and Chemical Toxicology,
- Enzyme-Protein Chemistry.

[28] They are accommodated in the Foundation's own premises situated at 48 Vassileos Constantinou Avenue (Athens).

Molecular Biology Programme

The research activities of the Molecular Biology Group of the IBRB focus on the role of nuclear ribonucleoprotein complexes (hRNP) in the regulation of gene expression at the post-transcriptional level, in higher eukaryotes. Current findings indicate the participation of nRNP constituents in almost every aspect of mRNA metabolism and, in addition, their involvement in pathological conditions, including autoimmunity and cancer. Our on-going scientific efforts relate to questions of both basic and applied research on the above aspects.

Molecular Endocrinology Programme

Research objectives of the Molecular Endocrinology Programme include the molecular mechanism of steroid hormone receptor function in health and disease and the role of heat shock proteins in regulating the transactivation potential of steroid receptors. Applied research objectives include the development of immunoassays for the assessment of steroid receptor levels in tumor biopsies and bioassays for estimating receptor activity in cultured tumour cells. The programme has been managing a facility committed to the analysis of oestrogen and progesterone receptor levels in tumours since 1981, with a yearly input of nearly 700 breast tumours from different breast clinics operating in and around Athens.

Programme of Chemical Carcinogenesis

The Programme of Chemical Carcinogenesis aims to develop the scientific basis for the assessment of the carcinogenic risks associated with human exposure to chemicals. In the context of the Programme, basic and applied research projects are being carried out which address questions related to the role of DNA damage and repair in the mechanism of chemical carcinogenesis as well as the utility of biological markers of individual exposure and susceptibility in the refinement of the process of risk assessment. Particular attention is paid to the category of methylating carcinogens which include food- and tobacco-associated N-nitroso compounds, chemicals of industrial and agricultural importance and pharmaceuticals. Furthermore, the genotoxic effects of constituents of urban air pollution on man are being investigated in the context of large-scale molecular epidemiology studies.

In addition to research per se, the programme (and the associated Unit of Environmental Toxicology) is involved in a range of activities in the wider field of environmental toxicology. These activities, which aim to support the work of regulatory and other agencies involved in public health protection, mainly include the bibliographical review of the toxicity of chemicals and the construction of bibliographical databases of environmental toxicology focussing on studies related to the Greek environment and population.

Gene Regulation Programme

The aim of the Gene Regulation Programme is to study cellular signal transduction molecules and mechanisms, in order to inhibit their deregulated function in disease. The research interests of the Gene Regulation Programme focus on the analysis of function of onco-transcription factors and their differences between normal and cancer cells.

More specifically, studies are performed concerning the regulation mechanisms of transcription factor families jun/fos (AP-1) and ets by mitogenic signals that are disturbed during the process towards tumour cell formation. Furthermore, the functional analysis of target genes and their products, which are involved in the invasive and metastatic procedure by degrading the extracellular matrix such as the matrix degrading metalloproteases (MMPs) and their inhibitors (TIMPs) regulated by AP-1 and ets transcription factors is under consideration.

Cellular Aging Programme

The Cellular Aging Programme focuses on the cloning and regulation of genes that are linked with aging and longevity. Several genes have been cloned that associate with cellular aging as they have been found overexpressed in senescent cells of different species and origins. These genes have been repressed in fully transformed cells raising the intriguing possibility of the existence of common molecular links between aging and cancer. Moreover as longevity may be controlled by "survival genes" a comprehensive study is currently being carried out by monitoring gene expression levels in samples derived from centenarians. In a complementary approach the molecular mechanism of cancer initiation and progression and hence the repression of the senescent phenotype is studied. Primary tumours and cell lines of breast and ovarian cancers, as well as from osteosarcomas are studied in relation to their in vitro chemosensitivity to several drugs. In addition, the expression levels of several genes, including oncogenes, growth-arrest-specific, drug-resistant and metastasis genes, are monitored before and after drug treatment to evaluate on a genetic level the reversion of the malignant phenotype.

Regulation of Protein Phosphorylation Programme

The main research objective is the study of cellular functions regulated by protein phosphorylation-dephosphorylation, the most important and ubiquitous post-translational modification regulatory mechanism, the isolation and characterization of protein kinases and phosphatases and the development of analytical methods for the determination of these catalytic actions. A major focus of the programme is the elucidation of the role of brain protein phosphorylation in the pathogenesis of neurodegenerative diseases (Alzheimer's disease) which will serve for therapeutic intervention.

Protein Structure, Function & Regulation Group

Proteins have a fundamental significance in all biological processes. The knowledge gained of their structure, function and regulation will provide an understanding of these processes with far-reaching consequences for human health. Our programme aims to understand proteins involved in two areas:

(1) control of glycogen metabolism-structure and function of glycogen phosphorylase and phosphorylase kinase (in collaboration with the Laboratory of Molecular Biophysics, University of Oxford). Understanding the regulation of glycogen metabolism is relevant to the design of new therapeutic agents to control elevated blood glucose levels in Type II diabetes.

(2) control of neuromuscular transmission-structure and function of Fab fragments of monoclonal antibodies directed against the main immunogenic region (MIR) of the nicotinic acetylcholine receptor. Knowledge of the structure of selected anti-MIR antibodies will be used for the rational design of antibody mutants as novel drugs in the treatment of myasthenia gravis.

Enzyme Technology Programme

The study of the metabolism of Lactic Acid Bacteria (LAB) is a part of the enzyme technology programme. This study is focused on two main research projects.

Firstly, the study of the proteolytic activity of LAB includes the isolation and characterization of a casein specific extracellular proteinase. Factors influencing the proteolytic activity in various growth conditions and media. Induction of the enzyme biosynthesis, proteinase regulation through post translational modification and the study of the role of phosphorylation in enzyme activity.

The second projects focuses on cholesterol uptake from selected strains of LAB, determination of the conditions maximizing the cholesterol uptake, the study of the enzymes involved to the cholesterol uptake, the study of the cholesterol metabolism in LAB and attempts of expression of the gene of the cholesterol reductase in LAB.

Biomimetics Programme

The Biomimetics Group deals with studies concerning the behaviour of biomolecules, such as enzymes, in model systems that simulate their natural environment. Structural and functional aspects of the biomolecules when hosted in restricted aqueous environments are characterized. Water-in-oil microemulsions can be considered as model systems for such studies, since they provide the possibility of solubilizing enzymes in water microphases compartmentalized in a hydrophobic solvent. Substances with different polarity can be localized in the distinct microphases and react through an enormous total interface. Microemulsions can be used to study enzymatic reactions of lipophilic substrates, membranic enzymes, or even for protection against denaturation.

Three main research programmes are developed: Structure and function of lipase in microemulsions; Activity studies of proteolytic enzymes in microemulsions; Structural studies of microemulsions by spectroscopical probing techniques. Many applied projects are developed in collaboration with partners from the food, pharmaceutical and cosmetics industries.

Applied Research & Development at the IBRB

In recent years, researchers in IBRB have reoriented their activities to include applied research projects and participate in regional development plans of our country and the European Union. Emphasis is also placed on their integration in E.C. programmes. This goal, which is based on the three main research areas of the IBRB, has led to the establishment of three applied research Units, which are aimed at product development and technology transfer to industry, government departments, hospitals, etc.

The three Units are the following:

- Molecular Biomedicine Unit,
- Chemical Toxicology Unit,
- Industrial Enzymology Unit.

4.7.3. Institute of Molecular Biology & Biotechnology (I.M.B.B.)

The Institute of Molecular Biology and Biotechnology (IMBB) was founded on May 1983 and was one of the —initially three— institutes of the Research Center of Crete (RCC). Since 1987, IMBB is one of the seven institutes of the only regional research foundation in Greece (FORTH). The first director of the IMBB was Prof. Fotis Kafatos.

In 1993, Prof. Kafatos was elected as the Director General of the EMBL (European Molecular Biology Laboratory in Heidelberg, Germany) and stepped down from the directorship of the Institute. He was succeeded by Prof. George Thireos, who was elected formally as the Director of IMBB on January 1994.

The IMBB is one of seven research institutes constituting the Foundation for Research and Technology - Hellas (FoRTH), and collaborates closely with the Department of Biology, University of Crete and the Science and Technology Park of Crete. IMBB has also been the Greek National EMBnet Node since 1989. The Institute is located in Crete, seven kilometers away from Heraklion, near Voutes.

The activities of the IMBB are aimed at high quality basic and applied research in attentively chosen fields of modern Molecular Biology and Biotechnology. The ultimate goal of these activities is the improvement of life quality through interventions in medicine, agriculture, industry and the environment. Areas of research include the elucidation of basic biological mechanisms and functions, ultimately related to human health, genome research, biological control of biological pests, enzyme structure and the development of high technology tools and products. These activities are successful through (1) the establishment of national and international competitive research networks and (2) collaborations with industry.

The research groups work in the following areas: Mammalian Molecular Genetics, Human genome mapping, developmental immunology and neurobiology, gene expression (MHC II genes, liver-specific genes), disease genes (tumour suppressor, anaemias, Alzheimer’s).

Let us now look in detail at the studies performed in each field:

- **Insect Molecular Genetics:** Drosophila genome mapping and sequencing, development and function of the nervous system, biological control of insect pests: (development of transformation system in Med fly and molecular biology of mosquitoes).
- **Molecular Biology Of Unicellular Organisms:** Yeast genome sequencing, systematic functional analysis of yeast genes, transcriptional control, stress responses, protein secretion mechanisms in bacteria, development of environmental biosensors.
- **Plant Molecular Biology:** Plant-pathogen interaction, pest control, molecular plant virology, viroids, gene suppression by ribozyme technology, disease-resistant plants.
- **Macromolecular Structures:**
  - Structure and function analysis of various families of proteins via X-ray crystallographic methods. The proteins studied include: electron transport systems, chitinases, endonucleases and DNA-methyltransferases.
  - Engineering and design of selected structural classes of proteins (4-alpha-helical bundles, alpha/beta barrels).

- **Enzyme Technology:** Bioconversion of chitin to chitosan, psychrophilic enzymes, DNA modification enzymes, separation technologies, downstream processing.
- **Applied Biochemistry and Immunology:** Human cellular and molecular immunology, peptide and antibody engineering, development of antibody and DNA-based diagnostic tools.

Activities related to the development and modelling of products include:

- Development and marketing of DNA restriction and modification enzymes, under the trademark MINOTECH;
- Marketing of DNA oligonucleotides produced in the Microchemistry laboratory;
- Development and marketing of enzyme immunoassay kits for the measurement of steroid hormones and receptors.

These products are supplied in the national and international markets in collaboration with companies, major ones include: Boehringer Mannheim (Germany), Pharmacia (U.S.A.), Quantum Biotechnologies (U.S.A.), Renner GmbH (Germany), Ciba-Geigy (Switzerland), Enviro Europa S.A. (Greece), Melotech S.A. (Spain).

Patents presented by the IMBB:

- “Eukaryotic Transposable Element”, (U.S. Patent No. 5,348,874).
- “Purified Chitin Deacetylase” (U.S. Patent No. 07/773,724, licensed).
- “Simple and rapid amplification and detection of nucleic acids”. (U.S. Patent serial No. 5,569,582).
- “Asymmetric hammerhead ribozymes and nucleotide sequences for their construction”. (PCT application PCT/EP93/02853, pending).
- “DNA encoding chitin deacetylase”. (U.S. Patent appl. No. 07/989,991).

The IMBB receives the following funds (in euros) for the development of its activities:

Competitive EU Grants (+matching funds)	1,985,730 euros
Other international grants	217,775 euros
National grants	682,750 euros
Sales of products	151,494 euros
Government Funds	954,500 euros

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4.7.4. MINOTECH biotechnology

MINOTECH biotechnology (Mb) started its operation in 1987 as an applied production unit of the Institute of Molecular Biology and Biotechnology (IMBB). Mb draws on the strength of the IMBB in protein purification and Molecular Biology.

Mb has an expanding line of high purity and superior quality reagents that aim to meet the needs of scientists engaged in Research, the Biotechnology Industry and the Clinical Laboratory. The present focus is on: recombinant DNA reagents (DNA restriction/modification enzymes, molecular biology kits, etc.); cytokines and their antibodies; specialty enzymes and their antibodies, and services (fermentation and protein purification).

Mb products have been successfully introduced into the Greek and international markets. Future plans include the expansion of its activities and the establishment of an independent private company.

At MINOTECH biotechnology, we are committed to excellence in recombinant protein production through elaborate protein expression and purification services. We produce polypeptides under contract for pharmaceutical, genomics, diagnostics and biotechnology companies as well as for individual research labs for use in high throughput screening, crystallography, cell biology and diagnostics. We offer services ranging from gene cloning to polypeptide purification. We can improve existing and develop new bioprocesses leading to improved polypeptide production and purification yields, optimised fermentation and gene expression protocols. We will help you increase your productivity and conserve precious internal resources.

The centre provides:

- Experience: hundreds of proteins produced ranging from restriction enzymes to human cytokines.
- Different expression systems: *E. coli, Streptomyces.*
- Capacity: milligram to gram quantities of purified protein.
- Quality: batch records and certificates of analysis with every lot (ISO 9001 certified).
- Confidentiality: work performed under strict confidentiality.

MINOTECH biotechnology offers a range of gene cloning and expression services for protein production using the following scheme. The Mb Five Step Protein Production path:

1. Clone gene.
2. Express protein.
3. Purify protein.
4. Test activity.
5. Scale-up process.

1. We clone the gene or full-length cDNA encoding your protein in appropriate vectors.
2. We can evaluate different hosts to identify an optimal system for production of your gene product. Polypeptides can be collected intracellularly (as soluble protein or insoluble inclusion bodies), in the periplasm, or as a secreted protein in the medium. Inclusion bodies material can be isolated and renatured using chaotropes. Refolding will be tested using CD, gel filtration, native page and enzymatic assay (if available).

3. Protein purification schemes can be developed. Depending on the polypeptide (concentration, stability etc.) and whether tags are present or not, various purification strategies can be devised. We aim to develop schemes involving the smallest possible number of steps. We can provide a few milligrams of purified material for enzymatic and/or biological testing.
4. Polypeptides may be tested on site using your assay system. Tools: fluorescence, colorimetric, radioisotope, surface *plasmon* resonance, immunoassay, HPLC.
5. Successful production can be scaled-up to fermentation scale (50L and 30L). For large-scale purification we use Pharmacia FPLC or Bio Pilot.

4.7.5. Mediterranean Agronomic Institute of Chania (MAICh)

The Mediterranean Agronomic Institute of Chania (MAICh) was created in accordance with Law 4443/64, which established Greece as a founder member of the International Centre for Advanced Mediterranean Agronomic Studies (CIHEAM). It was founded under Law 1537/85, which was passed by the Greek Parliament following the provision of Article 28, paragraph 1 of the Constitution (after at least a 2/3 majority of members voted in favour).

The Centre constitutes an international organisation whose aim is the development of scientific cooperation in the sectors of economics, rural development, management, and applied biological, technological and environmental sciences, addressing problems in the Mediterranean area. The Mediterranean Agronomic Institutes of Bari (Italy), Montpellier (France) and Saragossa (Spain) are constituent Institutes of the same organisation. The annual budget contribution of the Mediterranean Agronomic Institute of Chania is provided entirely by the Greek government.

An important comparative advantage accruing from the activities of the Mediterranean Agronomic Institute of Chania is that the competence in the development of cooperation is highlighted within the European Union, the Mediterranean basin and the Balkan countries, both in the provision of post-graduate training of executives and academics from these countries, as well as in the contribution to their economic development through common research and development projects.

Basic MAICh Activities[29]:

- MAICh assists the aims of the E.U. and Greek foreign policy, related to the Mediterranean and the Balkan countries, through the creation of common educational and research interests and the transfer of the comparative benefits connected with them.
- MAICh offers enhanced post-graduate education and research activities at *MSc* level to executive personnel from the countries of the broader Mediterranean basin. Its strength in such specialised scientific activities is attested by an output of about 150 graduates annually who are absorbed by the public and private sectors of these countries, forming the basis for cooperation between them, the E.U. and Greece.
- MAICh organises specialised courses and seminars both at its headquarters and in third countries of the Mediterranean and Balkan regions directed at executive employees through co-

[29] Web site: http://www.maich.gr/about/activities/

operation with the Ministry of Agriculture, Ministry of National Economy (Bilateral Development Assistance Cooperation, DAC), and EU (DGI), PHARE-TEMPUS programmes, etc.
- MAICh coordinates research networks, which address spearhead topics in European and/or Mediterranean countries.
- MAICh participates in the implementation of post-graduate programmes of pan-European character (SOCRATES -ERASMUS).
- MAICh contributes vigorously to the implementation of research policy in the Community strongly participating in pan-European joint ventures in competitive actions of the DGI, DGVI, DGXI, DGXII, DGXXIII. As a result, full advantage is gained from specialised manpower and opportunities for development are created for medium-sized enterprises.
- MAICh joins in the implementation of national research policy with participation in the activities inaugurated through the Community Support Framework, by the Ministry for Development, the General Secretariat for Research and Technology, as well as in application development actions carried out by the Ministries of National Economy (INTERREG), Agriculture, and Environment (LIFE), and the Regional Authority of Crete.
- MAICh contributes to regional and local development through innovative actions carried out by (ECOS-OVERTURE, Regional development programmes, Article 8 of FEOGA) etc.
- As a consequence of the programme of Euro-Mediterranean Partnership Cooperation (MEDA), MAICh has been afforded further opportunities and the multiplier effect of benefits from its activities has gained even greater weight. MAICh has already implemented actions, which are funded by an agreement on cooperation between CIHEAM-EU/DGI within the framework of MEDA.
- MAICh creates sources of self-funding from laboratory analyses, documentation services, and congresses facilities.

From the point of view of cost/benefit analysis of this social investment, adheres direct benefits which amount to an additional 80% increase of the value of the contribution of the Greek Government and the indirect benefits lead to educational, research and development of manifold value.

The co-operation project for the “Regional Action Plan” entitled “Conservation and Management of Natural Renewable Resources” between the European Union DGI/CIHEAM, for the period 1998-2002, has recently been approved and funded.

Among the budgetary lines, a study on Biotechnology has also been approved and is coordinated by the Mediterranean Agronomic Institute of Chania (MAICH). The aim of this study was to assess “Human and material resources allocated to priority issues for the region: Improving resistance to biotic and abiotic stress, post-harvest conservation, biosafety and property rights on innovations”.

To assess human and material resources on Plant Biotechnology in the Mediterranean region, with emphasis on the non-EU member countries, we developed and distributed widely a “Biotechnology questionnaire”. The questionnaire can be downloaded (format), completed and returned to MAICh to update the database. Since then, we have collected a number of replies to the questionnaire, visited several candidate partner institutions and scientists and discussed the current agricultural issues in which Biotechnology research can contribute, and finally consulted with the EU and CIHEAM officers responsible. The information collected from the questionnaire, will be tabulated in an electronic database that will become accessible via the Internet.

The Mediterranean Agronomic Institute of Chania has formed a research collaborative group composed of the following partner institutions:

- ICARDA (Syria)
- AGERI (Egypt)
- AUB (Lebanon)
- University of Ege (Turkey)
- IPGRI (Syrian Branch)

With the Development Objective to "Strengthen ongoing research activities in the Conservation and Management of natural resources in the Mediterranean basin through active collaboration among regional research institutions with complementary expertise in Plant Biotechnology".

4.8. BIOTECHNOLOGY IN EGYPT

4.8.1. Marketplace: challenges and opportunities

The Government of Egypt places great importance on the significant role the agricultural sector plays in the national economy.

Agriculture accounts for 20 percent of both GDP and total exports, and 34 percent of the total labour force. The agriculture sector contributes partly to Egypt's food requirements; the rest is achieved through imports such as wheat, meat, oil and other food commodities, which put pressure on the hard currency reserve of the country.

The agricultural sector has undertaken major steps to reform its economic policy program such as:

1. Gradual removal of governmental controls on farm output prices.
2. Increasing farmgate prices to cope with international prices.
3. Removal of farm input subsidies.
4. Removing governmental constraints on the private sector in importing and exporting agricultural crops.
5. Imposing limitations on state ownership of land and sale of new land to the private sector
6. Adjusting the land tenancy system.
7. Confining the role of the Ministry of Agriculture (MOA) to agricultural research, extension and economic policies.

As the government moves toward privatisation, transfer of technology to the private sector has occurred (for example, in vitro micropropagation of the virus-free potato). This shows the capacity and interest of the private sector to adopt new technology. Technology transfer is expected to grow dramatically in the short term, as the research programs become more product oriented.

One of the major targets for biotechnology in Egypt is the production of transgenic plants conferring resistance to biotic stresses resulting from pathogenic viruses, bacteria, fungi, and insect pests, and abiotic stresses such as salinity, drought, and high temperature. These biotic and abiotic constraints are major agricultural problems leading to serious yield losses in many economically important crops in Egypt.

The AGERI (Agricultural Genetic Engineering Research Institute) was established in 1990 at the Agricultural Research Center (ARC) to promote the transfer and application of this technology. AGERI aims to adopt the most recent technologies available worldwide to address problems facing agricultural development (Table 7).

Table 7: Examples of current plant genetic engineering research at AGERI/EGYPTI

Discipline	Potato	Tomato	Cotton	Maize	Bean	Cucurbits	Wheat	Banana	Date palm
Virus resistance		X			X	X		X	
Insect resistance	X	X	X	X					
Stress tolerance		X	X		X		X		
Genome mapping and fingerprinting		X		X					X
Fungal resistance		X		X	X				

4.8.2. Strategic Goals of the Agricultural Sector

The strategic aims of the Egyptian agricultural sector are:

1. Optimising crop returns per unit of land and water consumed,
2. Enhancing sustainability of resource use patterns and protection of the environment,
3. Bridging the food gap and achieving self-reliance,
4. Expanding foreign exchange earning from agricultural exports.

4.8.3. Opportunities for Deploying Modern Biotechnological Approaches[30]

The opportunities that will allow modern biotechnology to focus are:

1. Producing transgenic plants resistant to indigenous biotic and abiotic stress,
2. Reducing the use of agrochemicals and pesticides and their environmental risks,
3. Improving the nutritional quality of food crops,
4. Reducing the dependency on imported agricultural products (Seeds-Crops).

The private sector has access to biotechnology, and has invested heavily in research and development (R&D) of technology and the necessary ancillary expertise to bring a product to market. The competitive edge of a private company depends on the proprietary nature of its R&D and the protection offered by intellectual property laws.

A private company might engage in development of a product in conjunction with a developing country because it addresses a technical problem critical to its own product development, it

[30] It should be noted that, from the point of view of the Egyptian Focal Point, this section gives facts that are general and not particularly specific to Egypt.

presents an opportunity to enhance its public relations, or because it provides a window to an important market, technology, or germplasm of interest.

Developing country institutions may be interested in working with private companies to gain access to important technology, develop managerial and business expertise, build intellectual capacity, or form a partnership with an entity that has an existing capability to bring a product to market.

4.8.4. Pioneer Hi Bred/AGERI; a Private/Public Partnership

The relationship between AGERI, an Egyptian public sector institution, and Pioneer Hi-Bred, a U.S. private company, was forged through a relationship that involved common business interests. The importance of co-development of technology as opposed to technology transfer is especially pertinent in the case of Pioneer Hi-Bred's relationship with AGERI. In this partnership, a public sector institution was able to bring a significant contribution to the table. AGERI has isolated a number of strains of *Bacillus thuringiensis* (Bt) that had pesticidal activity of interest to a private sector company. AGERI filed a patent in Egypt on January 11, 1996 (No.019797) on a Bt-derived bioinsecticide against a wide range of insects, and in the United States on January 10,1997 (No.5178-3) on Bt isolates with broad spectrum activity.

AGERI also has a state-of-the-art biocontainment facility, and a team of trained scientists. AGERI can provide access to the local Egyptian market and the broader Middle East market, both of which are sufficiently developed to be attractive. In turn, Pioneer Hi-Bred came to the discussion table with technology as well as with marketing, regulatory, and legal expertise of value to AGERI.

AGERI has therefore initiated a partnership with Pioneer Hi-Bred through a USAID R&D grant to achieve the following:

1. Research and training for AGERI scientists to be trained at Pioneer/Iowa in methodologies relating to agricultural biotechnology.
2. Potential for product development; Pioneer was granted access to evaluate certain novel Bt proteins and genes patented by AGERI.

Four parties have signed this agreement: Pioneer-UsA, AGERI-Egypt, ABsP /MsU-UsA, and USAID-Cairo/Washington D.C. Both collaborators, Pioneer and AGERI, have provided inputs to this research and training effort.

Joint discoveries resulting from the work will be shared and patent rights will be sought according to the terms of the USAID agreement. Pioneer Hi-Bred will retain sole ownership of its proprietary Bt gene(s) and proprietary germplasm, and AGERI will retain sole ownership of its proprietary Bt gene(s). Under a separate agreement, AGERI granted material transfer agreements (MTAs) for Pioneer Hi-Bred to evaluate the Bt toxin protein. Options for possible commercial development of Maize have been also considered. This is one of the examples of USAID-sponsored collaboration.

4.8.5. BIOGRO/AGERI; a Business Partnership

A second model of moving research into commercial application has been made through the successful interaction between scientists at AGERI and the University of Wyoming, who have been involved in collaborative research studies on Bt for the past six years. The research efforts led to the development of a biological pesticide based on a highly potent strain of Bt isolated from the Nile Delta. This strain is extremely effective against a broad range of insects: Lepidoptera (moths), Coleoptera (beetles), and Diptera (mosquitoes). An additional significant feature of this strain is its capacity to kill nematodes.

AGERI has successfully managed to manufacture its first biopesticide, Agerin, based on the insecticidal bacterium *Bacillus thuringiensis.* Agerin is capable of protecting a broad range of important agricultural commodities, of controlling a number of biomedically significant pests, and has the potential for sales on a worldwide scale.

To fulfil its commitments to bringing research results into application and large-scale commercial distribution to the farmers, AGERI, in collaboration with a private investor, succeeded in establishing a commercial business entity under the name “BIOGRO International”. This company is responsible for the marketing of research results conducted in AGERI and will be in a position to sell AGERI products. This is essential to guarantee that sales revenue generated from product sales will be reinvested in the Institute to support the continuation of its activities.

It is envisaged that BIOGRO will link with the Genetic Engineering Services Unit (GESU), which was established at AGERI to work out any commercial agreements to benefit both the institute and BIOGRO. It will also allow the free flow of information and products related to genetic engineering to be produced by the institute for marketing purposes.

AGERI attaches a high priority to collaborating with the private sector, which will be fully informed of R&D in the field of genetic engineering and biotechnology in Egypt through the circulation of newsletters and reports, having representatives of the private sector participate in the design of product R&D, and representation of the private sector on the board of directors of AGERI.

As one of the leading institutions in agricultural genetic engineering in West Asia, North Africa, and the Middle East, AGERI is planning to share its know-how and experience with other countries within the framework of Technical Cooperation among Developing Countries (TCDC). This will be achieved through specialized workshops, seminars, and internships. The institute can also provide professional consultation in the field of molecular biology and agricultural genetic engineering.

4.8.6. Role of the CGIAR centres

The CGIAR centres could usefully expand their activities in the following areas, to further assist national institutes in the applications of modern biotechnology:

Biosafety

- Setting up regional links to share biosafety data and to pool information.
- Providing training and guidance on risk assessment and risk management issues.
- Providing technical training in biosafety reviews, prior to release.
- Building consensus among nations on biosafety protocols and guidelines.
- Assisting in the development of media and information materials to increase public awareness.

R&D collaboration

- Increasing CGIAR/NARS collaboration in biotechnology R&D.
- Setting up programs for the use and management of technology.

Intellectual property management

- Increasing awareness on intellectual property and its fundamentals (copyrights, trade-marks, patents, licensing, plant variety protection, plant breeders' rights)
- Establishing intellectual property policy and institutional policies
- Building capacity and human resources development in the field of technology transfer and intellectual property rights.

4.8.7. Other centres

AGERI has a major role in promoting biotechnology in Egypt, but it is not the only institution in the country interested in the subject. The National Research Centre, Universities and several Research and Development institutions, particularly in the pharmaceutical industry, carry out activities and have made achievements in the biotechnological field. No information on those centres is presented in this study.

4.9. BIOTECHNOLOGY IN CROATIA[31]

4.9.1. Croatian Program for Innovation and Technology

This Program is based on the experience of successful economic systems, but in some segments it has been adjusted considerably to conditions of Croatian economy and tradition:

- Research and development of new technologies, products, processes, services and markets have no alternative in the Croatian economy;

[31] From the point of view of the Croatian Focal Point, this section would be more complete if a list were provided of the biotechnology projects and activities that have been carried out by BICRO particularly and in Croatia in general, as well as the target industries of these projects and initiatives.

- Opening perspectives to human potentials, particularly those with higher education degrees, capable of their own personal involvement in the creation of relevant technological future;
- Integration of all research potentials ranging from higher education institutions, public institutes, economic institutes to individuals, including existing infrastructure and premises, as well as establishing new institutions, into a planned research activity that will result in feasible technological solutions and patents;
- Experience of developed countries shows that founding technology centres, technology parks for research and development, is by all means appropriate for Croatian conditions. It is the only correct way to decrease a gap among countries with developed and underdeveloped technology;
- Creating environment and infrastructure to support the establishment of knowledge-based small and medium enterprises;
- Establishing an efficient system to support the creation of new technologies, products, processes, services and markets;
- Change in a manner, philosophy of thinking, towards attitudes that would enable Croatian integration into the designing, creation and production of new products, technologies, processes, such as biotechnology, microtechnology and communication-information technology;
- Gathering and acting towards a mutual goal, —the technological development of Croatia— of all the actors that must and can contribute to this.

4.9.2. Business and Innovation Centre of Croatia (BICRO)

BICRO is a government institution, established by the Government of the Republic of Croatia, under direct jurisdiction and within the system of financial support of the Ministry, through co-financing operational costs (overheads), but not development.

This technology policy assigns BICRO a very important role in the implementation of the program for the creation and development of knowledge-based small and medium-sized enterprises. To be specific, these are tasks related to professional and financial monitoring of the creation, development and final formation of knowledge-based SMEs. In a full sense it implies overall assistance in the creation of the knowledge-based SMEs, including consultancy; analysis of the entrepreneurial plan, investment project, business strategy and organizational development; providing financial resources; identifying domestic and foreign partners during the foundation and final formation and marketing of its products or a whole company in Croatia and abroad. BICRO offers services that are similar to those offered to knowledge-based SMEs, to existing companies engaged in the transfer and improvement of technology, and to innovators.

The Government of the Republic of Croatia continually provides financial resources for this purpose. Co-financing is expected from regional and local communities and interested economic entities. In the implementation of this function BICRO relies considerably on Technology Innovation Centres, as well as on other public or private institutions, and they present a framework for the creation of a flexible and open network of transfer institutions focused towards the development of knowledge-based SMEs.

4.9.3. Instruments of Policy for Innovation and Technology

This technology policy provides for a planned state support to the orientation towards development of the knowledge-based SMEs. Its final products are economic and entrepreneurial advancement and results of planned scientific research. Instruments of technology policy are measures that will and may be modified or expanded, depending on the economic development and needs of the country:

- Regulations related to the knowledge-based SMEs;
- Technology Field Council at the Ministry;
- Financing scientific and developmental technology projects and research;
- Financing technology infrastructural institutions;
- Financial support for the founding, development and operation of knowledge-based small and medium enterprises;
- Promotion of knowledge-based entrepreneurship;
- Education, training for the needs of knowledge-based entrepreneurship;
- Support for the associations of knowledge-based SMEs;
- Support for “traditional” inventive and innovative activities.

Financing scientific and developmental technology projects and research is, in a full sense, financing the creation of Croatian product with a high proportion of intellectual work. Abundant financial resources would enable Croatian researchers to participate in the improvement of existing technologies, introduction and creation of new technologies, products, processes, services and markets. Financing is channelled through the Ministry, as a control mechanism of technological orientation and progress, recognizing full autonomy and freedom of research. The Ministry cooperates closely and accepts recommendations of the Research and Development Technology Institute in relation to allocation of funding for research at registered scientific-research organizations.

Financing technology infrastructural institutions is a direct assistance to development and functioning of those institutions through co-financing of necessary costs related to research. This assistance is obligatory, especially in the environment of a fragile economy. In addition, this logical co-financing is a control mechanism of the Ministry over those institutions in terms of limiting planned activities to research and technology and the creation, developing and operating knowledge-based SMEs. The Research and Development Technology Institute, and employees of institutes located in infrastructural institutions have a special way of financing. As stated earlier, their activities are financed completely by the Ministry. Such financing requires special authority of the Ministry, as regulated by the decree on the founding of the Research and Development Technology Institute.

Financial support for founding, development and operation of knowledge-based small and medium-sized enterprises is a new category, although the Government of the Republic of Croatia approved this idea in its conclusion dated March 18, 1998. It is an instrument, a technology policy measure that Croatia uses to join the economies of knowledge in the most direct way.

This measure provides a real support for entrepreneurial projects based on new technologies and products. Results of scientific and developmental research are implemented through the production activity of knowledge-based SMEs. Those financial resources support their founding, development and final formation. However, the logic of the economy lies not only in the introduction and creation of new technologies, products, processes, services, and markets, but also in the improvement of the existing ones. A portion of foreseen and secured financial resources is used for this purpose, i.e. for activities of existing companies outside technology centres. In addition, innovative ideas of individuals, innovators, are also financed from these resources up to the level of a prototype, in case the innovator, apart from his/her innovation, does not possess the entrepreneurial spirit to establish a company. The last two types of financing, innovative improvements and prototype solutions, become prominent for another reason and that is the fact that regional and local communities have to deal with the problems of existing local companies, and it is they, along with the state and the Government, that really finance technological development. That is to say that resources for described support are provided for in the state budget, budgets of regional and local administration and self-government, and interested economic entities.

Direct financial support from the state is used for example for direct loans, non-repayable funds for projects, guaranteed loans or other types of direct support. In order to secure instruments of public support for the introduction and creation of new products and technologies, specific financial instruments for their financing are created e.g. various investment funds, such as a seed-fund or risk-capital fund. Procedure and manner of use of resources and creation of funds, if necessary including other institutions from the region, will be regulated by separate legal acts. BICRO drafts such acts and submits them to the state administration. BICRO has jurisdiction for the actual implementation of the technology policy instrument.

4.9.4. Biotechnical Foundation. (Faculty of Food Technology, University of Zagreb)

The Biotechnical Foundation was constituted in 1996 during the celebration of the 40th Anniversary of the Faculty of Food Technology and Biotechnology, University of Zagreb. The Foundation was created with the following goals: promotion of biotechnology, food technology and nutrition, and environment protection. Its basic purposes are scholarships, awards and financial support for the best students and young researchers.

The Foundation has been initiated by mutual efforts of the Faculty of Food Technology and Biotechnology and industry. The role of quality experts in food processing and in nutritional evaluation, as well as in the application of biotechnical methods in food and drug industry and environment protection has been immense.

Industry, with its funds and financial support, directly promotes the education of future experts. The Biotechnical Foundation recommends the most creative student and researchers to the Foundation member companies as future workers or co-workers. The Foundation awards its financial support only to excellent regular students whose creativity has been expressed during their study period and has contributed to the economical improvement in Croatia.

The founder members of the Biotechnical Foundation are: Belupo, Coca Cola - Amatil, Daruvarska pivovara d.d., Buzetska pivovara d.d., Karlovačka pivovara d.d., Pliva d.d., Podravka d.d., Vindija d.d. and Zagrebačka pivovara d.d.

Biotechnical Foundation was registered in 1997 according to the Law on Foundations and it was entered under number 11 in the Foundations Register at the Croatian Department of Justice. The

Foundation is governed by the Board of Directors. There are also: Honorary Board of Directors, Chief Manager and Secretary. The Foundation has neither permanent employees, nor its own services.

The Foundation is based on founders' donations. According to the amounts donated the founders acquire the following statuses: permanent donator, honorary donator, donator or supporter.

Donations made each year to the Foundation by the donators form the basis of the Foundation funds. Awards, scholarships and financial support are financed from the funds interest. The funds are enlarged each year. All the donations, as well as all the Foundation activities, are regulated by special legal acts and provide many advantages and privileges.

Each year the Board of Directors plans a Foundation budget available for scholarships, awards and financial support. This amount is then donated to students, and the Foundation donator companies are informed about the results. All students are informed about the available scholarships, awards and financial support through a public contest. The Foundation, as a co-organizer of scientific meetings, can also reward the best young researchers for their original research results, which could be applied in industry.

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5. FUTURE INNOVATION: BIOLOGICAL RESOURCE CENTRES

Within the Mediterranean countries, France is perhaps the country that has the most developed biotechnological industry and on an administrative level, which means greater attention is paid to the problems and perspectives that this industry has. For this reason, it was also the first Mediterranean country to develop a plan with medium and long-term targets in this sector and to set up an Advisory Committee to keep track of it.

At the presentation of this Advisory Committee of Biological Resources, the French Minister of Research, Roger-Gérard Schwartzenberg, said the following[32]:

> "The Research Ministry has devoted much in-depth consideration to the matter of biological resources. The large body of work that has been accomplished in France has attracted deserved international attention and helped our country emerge as a pioneer in the organisation of Biological Resource Centres throughout the world. It is with great pleasure that I welcome you here so that we may further investigate how to create and promote these Resource Centres and successfully convince the international scientific community of this project's ethical and scientific merit."
>
> "A few ground rules must nevertheless be established to ensure the safe and effective use of the biological resources, and that national and international trade be organised and regulated so that France should not lose its competitive edge. It is for this purpose that we have decided to form a series of Biological Resource Centres (CRB) to be overseen by an Advisory Committee, which will be charged with a variety of responsibilities"[33].

In this chapter, we shall see in greater detail the reasons that led to the creation by France of this Committee and what repercussions this organisation may have on the development of biotechnology in the other countries of the Mediterranean.

5.1. THE IMPORTANCE OF BIOLOGICAL RESOURCES

There are at least four reasons why biological resources are important:

- Due to their great diversity and wealth, resources constitute a great heritage. The collections are reserves of genes that must be preserved and protected.
- In order to be able to study these resources, rigorous conditions of collection, preservation and accessibility are required.
- These resources present important legal questions, even in the international field, and, therefore, cannot be considered as being simply merchandise, especially in terms of traceability and biodiversity.

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[32] Web site: http://www.recherche.gouv.fr/discours/2001/ccrbiod.htm
[33] Paris, 22 February 2001.

- The resources are the starting point for biotechnological innovations in the field of health and the food and agriculture sector.

5.2. BIOLOGICAL RESOURCES CENTRES

Until now, these collections of organisms (microbial, vegetable, animal and human cells) as well as the elements of these organisms (tissue fragments, nucleic acids, proteins, etc.) were seen to be spread throughout different facilities: research centres, laboratories or hospitals. Gaining access to them was difficult and uncertain, and their use was uncontrolled. Facing this situation, it was important to bring these collections and their organisms, together, at Biological Resource Centres who would be in charge of purchasing, validating, studying and distributing such collections and organisms. In order to be able to carry out these operations in optimal conditions, four parameters must be taken into account:

- **Scientific rigour:** the research and study into the networks of genes involved in the functioning and dysfunction of cells and tissue require biological resources whose origins and quality are guaranteed.
- **Safety:** the diversity and the uncontrolled appearance of collections can involve health and environmental risks (the dissemination of pathogenic agents, for example).
- **Ethical requirements:** despite the existence of a legislative and regulatory framework on the use of collections for scientific purposes, this is not fully applied (especially when it is a question of biological resources of human origin).
- **Economic regulation:** currently, uncontrolled exchanges and irreversible losses take place. The formulation of specific standards in order to gain access to biological collections would favour scientific development and the development of rational industrial applications.

Biological Resource Centres have turned into strategic infrastructures for biotechnologies. Guaranteeing traceability and quality is indispensable, especially if we refer to the large number of possibilities offered by the analysis of the genome and post-genome studies: the identification of the interesting genes, modelling, diagnostic and therapeutic applications, biodiversity and emerging diseases.

Soon, a deontological code will be enforced, which will be subscribed to by Resource Centres that have human biological resources so that all procedures will be respected. This code regulates the origin of the samples and associated information; the conditioning, transformation, preservation, distribution and/or ceding of biological samples; copyright and promotion and the relationships between the different Biological Resource Centres.

The Ministry of Research awards the denomination of BRC (Biological Research Centre) to those Resource Centres that adhere to the deontological code. In this way, a coherent set will be established, organised by the Advisory Committee, whose mission will also be to establish relationships with the large institutions devoted to research.

5.3. THE ADVISORY COMMITTEE

In order to respond to the expectations of the scientific, medical and industrial communities, a Biological Resource Advisory Committee was set up. The budget assigned to the Committee for the year 2001 was 3.81 million euros and was supplied by the Fund for Research and Technology.

The budget is administered by a team made up of the Ministry of Research, representatives of the main French research institutions, three charity organisations (the AFM, the National Cancer League and the ARC), as well as the Franco-German EUROPROTEOME programme. Other members, like the Ministry of Health and the Agriculture Ministry are to join at a later date.

The Advisory Committee has to fulfil a dual mission:

- **To establish a national network of Biological Resource Centres** aiming to guarantee the quality and traceability of collections. The Committee will follow up the projects; it will favour the use of collections through the creation of consortiums where public research institutions, fund raising organisations and biotechnological industries come together.
- **To oversee the call for proposals** wishing to obtain the designation and financing of the BRCs that make up the network, co-ordinated with the research institutions that will manage projects. Thus, the INSERM has already announced a new bid aimed at favouring monocentre or multicentre research projects, which imply the creation of a new cohort or the use of one or several existing cohorts and the gathering of clinical and biological data (such as tissues, cells and nucleic acids). The projects must be executed within three years. The budget for the year 2001 was 2.1 million euros and was provided in equal parts by the INSERM and the Ministry of Research.

This device has meant that it has been possible to establish a procedure for the evaluation and accreditation of the BRCs. Moreover, it has favoured the development of infrastructures (storage and databanks); the assessment of the operative costs of the patrimonial collections, the obtaining of the necessary human and financial resources, bearing in mind that this may involve almost 200 patrimonial collections, and, finally, the co-ordination of these activities on a national level in order to increase quality and efficiency, and to offer greater international visibility, which is an essential factor.

5.4. INTERNATIONAL CONTEXT

Biological Resource Centres become relevant in the international framework. On 17 and 18 February 1999, in Tokyo, the OECD decided, at the request of some countries including France, to start research in order to study the conditions necessary to support the BRCs. The report of the study recommended a national system of accreditation, the harmonisation of rules and standards, transparency and the application of a broad BRC network on a world scale.

France developed a central function in these multilateral discussions thanks to its solid ethical standpoints and its collections which are a reference point, and whose quality is renowned the world over.

Due to all of the above, France was chosen to co-ordinate the mission that is being carried out by the OECD at Biological Resource Centres. This task requires the observation and control of the following key points:

- respect for the international commitments that are in force or being negotiated in this field,
- the States shall exercise their responsibility through suitable accreditation systems,

- the specific treatment of the resources of human origin,
- the participation of centres belonging to countries without the OECD,
- the rigorous supervision of quality and traceability,
- the upholding of France as the scientific reference point.

Furthermore, we should not forget the great responsibility involved in finding the balance between the excessively free circulation of biological samples, which could lead us to plundering the natural resources or the lack of respect for the principles concerning the concept of the individual, and the serious obstacles to know-how that can be raised, which would limit our capacity to progress in such fields as health.

This area deals with subjects which are especially relevant, such as a review of the laws on bioethics and the possibility of patenting inventions based on living organisms, which implies the search for a balance between the universal nature of world heritage and the results of human invention, which we should value proportionately.

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LIST OF WEBSITES

The Biotechnologic Gateway

http://strategis.ic.gc.ca/SSG/bo01376e.html

A Canadian page which talks in general terms about the biotechnological industry worldwide. It is a portal offering a great deal of information on products and services in all aspects of biotechnology. You can find Government Programmes, services, patents and other matters concerning the biotechnological industry of Canada. On the other hand, there is also a global vision of the uses of biotechnology, ethics and some applications of cleaner production in industry (paper, chemicals, textiles, food, energy, metallurgy and mining). This page was developed and is maintained by the life sciences sector of Canadian Industry.

Biotecnológica

http://www.biotecnologica.com

Biotecnológica is a portal of resources on biotechnology in Spanish where you can find articles, company databases, centres and bibliographical references, a news bulletin, links, and a discussion forum.

BIO-WISE Biotechnology at work

http://www.biowise.org.uk/

BIO-WISE is a programme of the Government of the United Kingdom which helps to improve the competitiveness of industry in the UK through the use of biotechnology and it supports the development of the industry of biotechnological supplies. Among other activities, BIO-WISE advises, offers free publications on the benefits of biotechnology, guarantees support to the companies that take part in biotechnology programmes, organises functions to present biotechnological opportunities and provides information and help for biotechnology supply companies.

EuropaBio (The European Association for Bioindustries)

http://www.europabio.org

EuropaBio is an association of bioindustries, representing almost 40 multinational members and 13 national associations (some 500 SMEs in all) involved in research, development, assays, production, marketing, sales and the distribution of biotechnological products and services in the fields of health, agriculture, food and the environment.

The European Association for Higher Education in Biotechnology (HeduBT)

http://www.eurodoctor.it/index.html

This association awards doctoral qualifications and a masters degree in Biotechnology in recognition of the exceptional quality of the prizewinners within Europe. This is achieved by making the doctoral or masters degree student acquire in-depth knowledge through courses in Engineering, Management, Computing, Economics, International Law and Ethics in Biotechnology.

European Integrated Pollution Prevention and Control Bureau

http://eippcb.jrc.es/pages/FActivities.htm

This website contains information on the industrial sectors, people and institutions involved in clean production, the information used in this field and the reference documentation. Among other services are the BAT documents *(best available techniques)* for each industrial sector.

France Biotech

http://www.france-biotech.org

France Biotech is an association created to stimulate and boost the development of the biotechnological industry in France. The association aims to prepare the way for the revolution in life sciences and create a favourable climate for the development of a strong French biotechnology industry.

Academic Info

http://academicinfo.net/biotech.html

Academic Info is a directory of Internet matters, which aims to become an important educational resource for the academic community.

Biotechnology in food and agriculture (FAO)

http://www.fao.org/biotech/

The FAO (United Nations' Food and Agriculture Organisation) was founded in 1945 with the aim of raising the levels of nutrition and standards of living and improving the agricultural productivity and conditions of rural populations. The website contains a glossary of biotechnological subjects and genetic engineering.

Biotechnology Information Directory Section

http://www.cato.com/biotech/

This website contains some 1,000 addresses of companies, research institutes, universities, sources of information and specialised dictionaries concerning biotechnology, pharmaceutical development and other related fields. Special emphasis is given to the development of products, the delivery of products and to services.

The Bioinfo Centre

http://dmoz.org/World/Espa%f1ol/Ciencia_y_tecnolog%eda/

The Bioinfo centre offers information on biotechnology, such as definitions, background, fields within biotechnology and the turnover of companies in the sector, among other information.

Por qué Biotecnología – The biotechnology portal in Spanish

http://www.porquebiotecnologia.com

This Argentinian website deals with the field of biotechnology, especially in regard to the dissemination of information to the general public. It includes, among others, basic concepts and questions, a glossary, activities and news concerning biotechnology.