ICSTI IRELAND

Irish Council for Science, Technology and Innovation

Technology Foresight Ireland

Report of the Health and Life Sciences Panel

Forfás

Established by the Government and Forfás to advise on Science, Technology and Innovation

Executive Summary

Health and Life Sciences

Ireland will need to invest even further in its greatest asset, that is, its emerging population of young and well educated people, if it is to maximise the benefits from knowledge-based industries in the coming decades. Attractive, high quality jobs will need to be created that fulfil the desires and expectations of these young people in order to keep them in Ireland and sustain a vibrant economy, the onset of which is just becoming apparent. The health and life sciences industries are capable of providing a high proportion of these jobs and the Irish educational systems are capable of generating the quantity and quality of the necessary employees, provided that certain conditions and strategies are fulfilled.

The Health and Life Sciences Panel seeks to address these conditions and strategies.

The Key Components

The Health and Life Sciences comprise all the biological sciences supported by large sections of complementary sciences and technologies. There are seven major sectors involved, which are extremely important to the Irish economy. These are:

a. Pharmaceuticals and Healthcare

b. Food and Drink

c. Agriculture, Forestry and Fisheries

d. Environment

e. Regulatory Affairs and Law Enforcement (through forensic science)

f. Information Technology (through e.g. bioinformatics, telemedicine)

g. Medical Devices (especially biomaterials)

The Panel, in consultation with many representatives from the above sectors, has agreed that one horizontal technology is radically influencing the global development of the health and life science industries i.e. **Biotechnology.**

The 21st Century – *'The Age of Biotechnology'*

Virtually all analysts predict that biotechnology is the basis for major economic growth. According to the National Science & Technology Council of the US, biotechnology

"....may well play as pivotal a role in social and industrial advancement over the next 10 to 20 years as did physics and chemistry in the post-World War II period" (source: Biotechnology for the 21st century - New Horizons. National Science & Technology Council, Washington, US, 1995.)

Bill Gates, founder of Microsoft, stated:

"I'm a big believer in information technology, ..., but it's hard to argue that the emerging medical revolution, spearheaded by the biotechnology industry, is any less important..." (Genetic Engineering News, March 1, 1997, p4).

Modern biotechnology originated in the early seventies and has since evolved rapidly to become an industry worth more than an estimated Euro40 billion in 1995 and providing between 300,000 and 400,000 jobs in Europe alone. A study, conducted in 1997 by EuropaBio, has predicted that this will rise to Euro250 billion by the year 2005 and affect in the region of three million jobs. If Ireland participates fully and proportionately, biotechnology will make a significant additional contribution to Irish GDP and job creation.

As Dr. E. Magnien, Director of Biotechnology, European Commission DG XII, recently stated:

"The life sciences are going to be (more than ever) an objective ally of socio-economic developments, in particular through future products and services...... But the background knowledge, unlike that which forms the basis of computer sciences, communication technologies, solar technologies or material sciences, is immense and all-embracing."

Ireland's Role

A second phase of biotechnological development is becoming evident, that is, a transition to genomics. Ireland, with the appropriate investments, is well placed to enter this phase and eventually to take a leading position. Biotechnology and genomics are particularly suitable to Ireland and Ireland is particularly suitable to these technological and environmentally-friendly industries for the following reasons:

The major components of the health and life sciences industry (pharmaceuticals, chemicals, agriculture, fisheries, food and drink, environment, forensic science etc.) are well established in Ireland and account for significant employment, exports and revenue. All these sectors are in transition and the new developments are strongly influenced by biotechnology.

- Ireland has succeeded in attracting a large pharmaceutical manufacturing sector, employing 12,000 people in 80 companies. Nine of the top ten companies in the world have manufacturing operations in Ireland. Of the present global pharma-products, an estimated 16 per cent are of biotechnological origin or are related to biotechnology; this is expected to rise to 30 per cent by 2005.
- The chemical industry is important, comprising about 45 companies and employing approximately 4,000 people. Pharma/chem is the second largest export sector in Ireland after engineering/ electronics and represents about 20 per cent of manufactured goods exported (exports for the pharma/chem amounted to IR£6,380 million in 1996, of which IR£4,890 million were from the pharmaceutical sector). The effects of biotechnology on the chemical industry can be seen in many ways. For example, chemical companies are using biotechnology to develop novel manufacturing processes. They are developing clean biodegradable biological compounds as substitutes for 'dirty' chemicals. Some chemical companies are gradually moving out of the chemical industry altogether and into biotechnology.
- The food and drink industry in Ireland employs 40,000 people and accounted for 31 per cent of GNP in 1997. Some Irish companies are world market leaders. Total exports in 1996 were IR£4.1 billion.
- Agriculture is being revolutionised and the effects are spreading world-wide. For example, genetically engineered soybeans will provide 50 per cent of Argentina's 1998/99 soybean crop and this figure is expected to rise to 80 per cent by 2000/01. Argentina is the world's third largest soybean producer, after the United States and Brazil.

- The biotechnology industry is highly research oriented. Irish institutes and universities have quite well-established biotechnology programmes. However, the research and education infrastructure needs to be significantly improved if Ireland is to keep pace and create a thriving biotechnology sector.
- BioResearch Ireland (BRI) has established the infrastructure for managing the commercialisation of research output from Irish universities. These mechanisms can be enhanced and improved.
- IBEC has formed the Irish Bio-Industries Association (IBIA) in order to improve the awareness of biotechnology and to meet the needs of the Irish biotechnology industry.
- Ireland has a very strong software industry. There are huge synergistic opportunities available to Ireland through combining its expertise in health and life sciences with its expertise in information technology. There is the potential to develop strong information based bioinformatic companies which rely on their access to knowledge and their ability to interpret and apply it, for their competitive success. In other words, knowledge intensive industries which combine computer science and biology.

Recommendations

The Health and Life Sciences Panel strongly believes that a biotechnology infrastructure can be created in Ireland. The Government must immediately invest, on a realistic scale, in a co-ordinated biotechnology programme which builds strong links between the universities, industry and agriculture, and the financial and services sectors, as outlined in this report. If this investment does not occur, Ireland will not only fail to benefit from the new biotechnology in terms of a large number of new, high quality, high added value jobs, but many existing jobs in the pharmaceutical and chemical industries, the food and drink industries and in agriculture will be jeopardised.

It recommends that a biotechnology infrastructure be built by a series of related strategic investments, herein referred to as The Irish National Biotechnology Investment Programme.

The Irish Biotechnology Investment Programme	
There are five sub-programmes:	
Biotechnology R&D Programme	- to provide technology, knowledge and expertise
Biotechnology Translational Programme	- to ensure that the technology, knowledge are commercialised
Biotechnology Start-up Programme	- to assist the start-up of indigenous bio-industries
Biotechnology Inward Investment Programme	- to develop multinational R&D programmes in Ireland
National Conversation on Biotechnology	- to increase public awareness

The Irish National Biotechnology Investment Programme will create an infrastructure with strong links and feedback mechanisms joining government, universities, high technology industries and the financial (e.g. venture capital) and service (e.g. patent agents) industries. The biotechnology infrastructure will allow Ireland to participate in the European biotechnology revolution. The Irish National Biotechnology Investment Programme will require an investment by government on a scale which matches the public investment programmes of the leading OECD countries in which biotechnology has become established. This investment is much larger than anything which has been considered previously.

We need to create new biotechnology industries as well as protecting and consolidating those older industries which are being threatened by biotechnology. The biotechnology programme will be a critical factor in helping to anchor and reform the pharmaceutical and chemical industries, the food and drink industries and to protect Irish agriculture. This programme will become increasingly important as the biotechnology industry grows world-wide and this is occurring at an astonishing pace. The biggest effects are already being seen in the pharmaceutical industry and in agriculture which are vital components of the Irish economy.

'Cluster Development'

The primary aim of this programme is to create so-called clustering conditions which have established viable biotechnology sectors in the United States, United Kingdom, Germany and Denmark. Most research on clustering in the biotechnology sector has led to the conclusion that the following conditions are necessary:

- a strong academic base with high quality R&D output, some of which is world class
- the right environment for translation of research output to innovation to company to product to market
- an adequate labour and knowledge pool
- an adequate base of those who can service and supply the sector
- an appropriate industry infrastructure
- a positive government policy towards the industry
- protection of intellectual property
- availability of equity and finance.

If the recommendations made by the Panel are followed, there is an exceptionally good chance that a biotechnology cluster can be developed in Ireland. With cluster development comes the desired outcome of additional employment and wealth creation. If a critical mass is achieved, the cluster will become self-standing and the necessity for positive government intervention will recede in time. However, it is important to realise that significant government support both through the supply of the right type of infrastructure and through finance is important at the start, otherwise it is very unlikely that the cluster will ever get off the ground and be self-sustaining.

The infrastructure will be essential if Ireland is to attract new biotechnology companies from abroad. The same infrastructure will enable the foundation of start-up Irish biotechnology companies and help to ensure they are sustained in the difficult transition to venture capital and the stock market. The biotechnology infrastructure will be important in facilitating the gradual mergers of, or alliances between, significant parts of the food and pharmaceutical industries. It will play an important role as Irish agriculture adapts to changes in the Common Agricultural Policy. In summary, an integrated biotechnology infrastructure will result in Ireland having a much larger, more powerful, stable health and life sciences industry and service sector, which will be strongly rooted in Irish brain-power.

The rewards will be the development of a sector of industry with very significant growth potential and with a high relevance to our existing mix of healthcare and agribusiness. This sector has an excellent 'fit' with the current output of graduates and with R&D programmes of the universities, albeit that these need very significant investment. If we invest wisely and adequately in our health and life sciences infrastructure over the next 10-15 years, as outlined in this report in which we draw heavily on the experiences of the United States (other European countries are doing likewise), biotechnology will be able to offer many challenging new high technology positions for students entering the labour market in the years up to 2015 and beyond. Following the EuropaBio report, Irish biotechnology jobs can increase at least ten fold over this period.

The Irish Biotechnology R&D Programme

Biotechnology is highly dependent on a competitive research base. To compete, Ireland must invest. However, much of the infrastructure, including significant facilities and skills, is already in place. An R&D investment is therefore being made within a reasonably well developed system. A significant programme is needed to develop a core of R&D activity in Ireland. Separate R&D programmes would be designed for start-up companies and other companies.

The output of this investment will be:

a. a flow of highly qualified, inventive, entrepreneurial biotechnologists

b. a flow of discoveries, technologies and ideas on which products, processes and services can be developed by Irish and Irish-based international industry

c. a level of activity which will raise Ireland's profile in this field, with benefits to all of the other objectives of the programme.

These objectives can only be created through a significant national biotechnology/bioscience competitive research programme, at peak training 400 research scientists per year for industry.

Such a programme would be designed to carry out 'leading edge' R&D in the biosciences and biotechnology relevant to medicine, industry, agriculture, fisheries, forestry and the environment.

The programme might have 100 groups in biomedical science (infectious disease, virology, microbiology, parisitology, heart disease, inflammatory disease, autoimmune disease, neurodegenerative disease, ageing, cancer, genetic disease including obesity and allergies, neuropsychiatric disease, drug addiction, preventative medicine, environmental epidemiology); 60 groups in agribiotech and food biotechnology (vegetables and crops, fish and shellfish, food processing and nutrition, food microbiology and food safety, animal and plant pathogens); 20 groups in IT, bioinformatics, genomics, proteomics, enzymology and drug discovery; 10 groups in environmental regulation, pollution waste disposal, re-cycling and bioenergy production; and 10 groups in instrumentation (DNA chips), biomaterials (e.g. polyhydroxybutyrate) and drug delivery.

Research projects within this R&D programme would be decided on the basis of proposals from researchers which would be assessed by international panels.

For this programme to be effective and produce research output of the standard necessary to contribute to a competitive research and industry base in biotechnology, it is vital that an effective performance evaluation system is put in place (details of which are outlined in section 2.4.1 of this report).

The Irish Biotechnology 'Translational' Programme

An increased pool of research activity must be matched with an additional focus on the commercialisation of research output, and specifically on developing links between industry and researchers, and on the formation of start-up companies based on the technology. This function is already performed by BioResearch Ireland (BRI) which was established in 1987 as a partnership with the universities. BRI was designed to facilitate generation of ideas and opportunities, and their commercialisation. The universities contribute their facilities and the ideas of their staff. BRI provides funding and innovation management expertise. BRI runs centres within five universities in which research and commercialisation activities are conducted. The activities of all centres are co-ordinated and controlled by a central BRI management team with expertise in patents and licensing, marketing, business development, product management and finance. This team is closely integrated with centre colleagues, and a strong corporate identity has been established within the organisation.

This activity, and other initiatives which result in research outputs or expertise being converted to economic benefit, is an important component of the overall programme.

The Irish Biotechnology Start-Up Programme

Enterprise Ireland should establish the Irish Biotechnology Start-Up Programme to invest in biotechnology companies which are in the early stages of development. BioResearch Ireland's experience has shown that viable technologies, with patent protection and with data to show their validity, still require a phase where company staff are identified, partners found and the company plans developed. This seed-stage requires a funding and management input which is almost entirely absent at the moment. This is an important component of an Irish programme.

The objective should be to support up to 50 biotechnology start-ups in the next 15 years.

Biotechnology Inward Investment Programme

The Irish pharmaceutical industry is a vital national asset. This industry is dominated by multinationals and links Ireland to the international pharmaceutical industry, the leading player in the biotechnology revolution. Nine of the top ten multinational pharmaceutical companies have major manufacturing operations in Ireland. This situation has great significance for the development of biotechnology in Ireland.

A deficiency of the Irish biotechnology system is the relatively small scale of the sector. One of the ways in which we can address this is to promote further activity by existing foreign industry across all functional components of companies including research, technical support and manufacturing. We should also attract further foreign biotechnology enterprises to Ireland. This will have beneficial effects on the sector similar to those seen in other sectors in the past, i.e. it will train and give experience to Irish graduates, and it will support the development of biotechnology service industries. A few lead companies could have a disproportionately positive effect.

Ireland needs to create an international image as a focus for biotechnology. Attraction of some international biotechnology companies would be a significant advantage. We need to devise a very strong financial and tax package for this purpose.

IDA Ireland should be given a specific remit to market Ireland as a location for biotechnology inward investment. Their target markets should be the US, UK and Germany. As biotechnology moves from phase 2 and 3 clinical trials to manufacturing, Ireland must exploit its existing expertise in pharmaceutical manufacturing to attract these companies.

The Irish National Conversation on Biotechnology

There is a need to consider ways of dealing with the pressures which are created between public demand for products/processes that enhance the quality of life and public concerns about the long term effects of genetically modified products/ processes. There is a potential for conflict between the demand by industry and the research community to move forward and capitalise on the economic opportunities presented by biotechnology and those who advocate a broader perspective that would take into account the long term social/environmental/ethical/safety impacts of these types of technological developments. It is incumbent on those who work in the field to get involved in a scientific manner in the public debate on the issues. The need to have a communications strategy in biotechnology that uses a partnership approach with ongoing, transparent and open dialogue should be a priority of any initiative. It should aim to increase public awareness and participation, information, communication and confidence.

Role of Biotechnolgy in the Health and Life Sciences

1.1 Introduction

The future of the Irish economy will be strongly influenced by the extent to which it is able to optimise the development of sustainable, environmentally-friendly, high technology industries over the next 15 years.

Biotechnology is the main high technology driver affecting the health and life sciences industry.

High technology industry is an outgrowth of the international R&D system. If Ireland has a strong indigenous R&D system, modelled on international best practice, high technology industry will grow faster and be more strongly embedded in Ireland. An Irish high technology infrastructure will create knowledgeable people who will staff and create knowledge-based business and industry. Such business and industry will be more likely to stay and develop in Ireland if the brain power is Irish and it will act as a magnet to similar industry from abroad.

A single example makes the point. The Massachusetts Institute of Technology (MIT) has created 4,000 companies over the last 30-40 years. These companies have an annual turnover of $230 billion and employ 1.1 million people (Professor Borge Diderichsen; Director of Corporate Research Affairs, Novo Nordisk plc, Denmark; Seminar TCD, July 1998). MIT, a private university, was and is one of the largest recipients of US government funds for R&D. The US has become the world leader in high technology industry because there are strong feedback loops (R&D programmes, tax incentives, patent laws etc.) joining government, universities and high technology industries. These loops are weaker in Europe and particularly so in Ireland. Ireland should examine and learn from the US model how to create sustainable high technology jobs. This model is being followed in other OECD countries, notably Denmark and Germany.

This report relates the potential to create a valuable industry to the need to invest both in research and in company development (both inward investment and indigenous).

1.2 The Health and Life sciences

The health and life sciences comprise all biology (including medicine, agriculture, food science etc.) and large parts of other sciences which interact with biology (chemistry, computer science, engineering, materials science, forensic science etc.). Recent discoveries in these sciences, which have been exploited mainly through the new biotechnology industry and its alliances, are already impacting strongly on seven major sectors which are important in the Irish economy, namely:

a. the pharmaceutical and healthcare industry

b. the food and drink industry

c. agriculture (and to a lesser extent forestry and fisheries)

d. environment (mainly through monitoring systems)

e. regulatory affairs and law enforcement (through forensic science)

f. information technology (through e.g. bioinformatics, telemedicine)

g. medical devices (especially biomaterials)

Biological industries account for a high proportion of Irish high technology jobs and a high proportion of Irish exports. These industries are being revolutionised world-wide by biotechnology.

Biotechnology is defined as 'the application of scientific and engineering principles to the processing of materials by biological agents'.

Biotechnology went through a development phase in the 1980s and is now going into a huge expansion, driven by genomics, DNA chips, combinatorial chemistry, phage display libraries, the polymerase chain reaction, robotics and many other high impact technologies which are now producing a torrent of new data.

"As a result of the human genome project and others we will have the ability to ask (and answer) questions based on large amounts of data..... Biology has great vitality, is important to society, and is in the midst of a revolution" Steve Koonin, Vice-President and Provost, Professor of Theoretical Physics, California Institute of Technology (Caltech News 32 no. 2, 1998).

No country with a strong food and pharmaceutical industry can afford to ignore the new biotechnology.

1.3 The 21st century - 'the age of biotechnology'

It is widely believed that biotechnology will be one of the most significant technologies of the early decades of the 21st century.

Bill Gates, founder of Microsoft, stated *"I'm a big believer in information technology, ..., but it's hard to argue that the emerging medical revolution, spearheaded by the biotechnology industry, is any less important..."* (Genetic Engineering News, March 1, 1997, p4).

According to the National Science & Technology Council of the US, biotechnology

"....may well play as pivotal a role in social and industrial advancement over the next 10 to 20 years as did physics and chemistry in the post-World War II period" (source: Biotechnology for the 21st century - New Horizons. National Science & Technology Council, Washington, US, 1995.)

The EuropaBio Report of 1997 noted that the

"the value of products and services using biotechnology in Europe could reach EURO250 billion by 2005 and affect more than three million jobs". (Benchmarking the Competitiveness of Biotechnology in Europe An Independent Report for Europabio June 1997)

In seeking to establish a dynamic, competitive, knowledge-based economy, characterised by a high skill base and high added value, Ireland needs to recognise that biotechnology is going to reveal more knowledge in the coming decades than all other technologies combined.

This prediction arises from two facts. First, plants and animals contain a virtually infinite and evolving store of knowledge within the genetic, biochemical, cellular and physiological systems of each species and their ecosystems. Every plant and animal has a vast library of biological information which we can search for useful knowledge. Second, we now have the tools to find this knowledge, to analyse it and to utilise it. There has been a revolution in biotechnology caused by a single invention, perfected in the early 1990s - automated DNA sequencing.

DNA sequencing is the basis of the science of genomics and is by far the most significant of the tools used to obtain biotechnological data. Bioinformatics and proteomics are by far the most important tools for analysis. The biotechnology companies have other tools that are needed to utilise the knowledge.

1.4 The biotechnology revolution: the pace of change

The 1984 report on 'Commercial Biotechnology: An International Analysis' to the United States Congress, was published by the Office of Technology Assessment and was very influential in promoting biotechnology in the US and world-wide. If anything, it underestimated the pace of change in the technology, especially the impact of DNA sequencing and bioinformatics. The report did not forecast the explosion in sequence data which has occurred in the last few years. It did not mention the words genomics, bioinformatics or proteomics. There was no hint of phage display libraries, automated DNA sequencing, the polymerase chain reaction or the DNA chip.

On its own, the Human Genome Project, which will produce the complete human genetic code (DNA sequence) by 2005, will contain three billion pieces of raw information and reveal the basic structure of at least 100,000 new genes which specify 100,000 new biological chemicals every one of which will have some medical significance.

"The great challenge for biology in the next century is to understand how each gene works individually and collectively to create a living organism" (Wellcome News, Issue 16, (1998))

As John Sulston, Director of the Sanger Centre, Cambridge, says: *"You have to remember that the sequence is only the beginning. It creates far more questions than it answers - it doesn't actually answer any biological questions at all. What it does is to provide a very finely honed set of tools for people to turn biological questions into molecular terms"*. (Wellcome News, Issue 16, (1998))

For example, this will include information that will lead us to a molecular and cellular model of how the brain works. On its own, the impact of this model on our understanding of all kinds of human thinking, education, brain damage, psychiatric disorders, ageing, etc. is certain to be substantial.

Other genome projects, some complete and some under way, for example rice, TB, HIV, leprosy and baker's yeast, are yielding huge amounts of information which will be useful in medicine, agriculture and industry. The raw data has a doubling time of eight months and the doubling time is falling.

The biological information explosion has some important characteristics:

i. the raw data (DNA sequence data), often in the public domain, are virtually useless
ii. primary data analysis requires sophisticated computation by molecular biologists
iii. there are not enough computer competent molecular biologists (bioinformaticians) in the world to carry out the primary analysis
iv. there are not enough molecular biologists to do the proteomics (gene to function)
v. the data are meaningless in the absence of top quality biology.

"Genomics now allows us to study, design and build biologically important molecules. As new discoveries in this arena are applied, companies and industries are being restructured in a way that will change the world's economy. Thus, this new science of genomics is forcing some of the world's largest companies to re-invent themselves as borders between

pharmaceutical, biotechnology, agricultural, food, chemical, cosmetic, environmental, energy and computer industries blur and erode. .... The flow of genomics information is so massive that it threatens to overwhelm existing R&D budgets, labs, and knowledge bases. It is driving megamergers...... Genomics has substantial government support, massive corporate investment, powerful enabling technologies" (Enriquez, J. Science 281, (1998) 925 Genomics and the world economy).

The table below shows some of the new technologies which are being used and some of the most important research themes. A more detailed (and technical) description of these areas is presented in Appendix III.

Some Important Technologies	Some Important Research themes
Genomics	Gene Function in Disease
Functional Genomics	Gene Transcription Factors
Gene Chip Technology	Signal Transduction
Knockouts and Transgenics	Apoptosis
Bioinformatics	Development Biology
Combinatorial Chemistry	Gene Therapy
Robotics and Screening Technology	Antisense Therapy
Screen Development	Immunotherapy
IT/Biotech Convergence	Microbial Genetics
Proteomics	Pharmacogenomics
Nem Diagnostics	Tissue Engineering
Drug Delivery technology	Therapeutic Antibodies
Biosensors	Free Radical Biology
Bioremediation	Plant Biotechnology Neurobiology Nutriceuticals Pharmaceuticals

The situation is literally 'all hands on deck'. There are not enough scientists, businesses or capital to take advantage of the extraordinary opportunities for discovery and commercialisation in the new biotechnology. Huge corporations are being assembled by mergers which are changing the face of the global economy and they are recruiting business and science partners world-wide. The simple conclusion is that there is a huge opportunity for Ireland to join in, to contribute to and to benefit from the next phase of the biotechnology revolution.

As we show below, Ireland is well placed to participate in the new biotechnology, but the pace of change is rapidly accelerating. While Ireland may not be too far behind in 1998, in another five years the gap will be enormous and well beyond bridging both financially and academically.

1.5 The US model

The United States has shown that a biotechnology industry cannot be created without highly competitive biotechnologists. In the United States these biotechnologists have been and are being produced mainly through government and industry funded R&D programmes at the universities. Of course these R&D programmes also provide much of the information and many of the ideas which are the feed stock for the industry. Many US entrepreneurs are scientists who started their careers as researchers, participating in government funded or industry funded R&D programmes. These people took their ideas and discoveries out of the laboratories into start-up companies which were an important element in the biotechnology revolution.

1.5.1 US Government strategy: past and present

The US leads in biotechnology because US university scientists invented it, US entrepreneurs and university scientists commercialised it and the US pharmaceutical and chemical industries have taken it over and developed it. The comparisons with the semi-conductor and microelectronics industry should be noted. The same alliance of US government, US science and technology and US business which brought us the microelectronics and information technology (IT) industry decided that biotechnology had the same potential as microelectronics and IT.

“The actions of the US government (mostly through the defence budget) that influenced the development of the US semiconductor industry were many and diverse. Undoubtedly, not all the effects of the Federal Government were intended or anticipated. With the benefit of hindsight, however, it is apparent that these actions helped to produce a dynamic, healthy US semiconductor industry. Similar actions by the Federal Government could encourage the development of companies in other high-technology fields such as biotechnology”. (OTA Report 1984)

Biotechnology emerged from molecular genetic research in US universities in 1970-1972. The OTA report noted that *“Federally funded research in the United States has been essential to the development of biotechnology”* and that most of this had been conducted at non-governmental laboratories especially at research universities. Biotechnology became the key driver in the health and life sciences industries and services in the US in the 1980s. The US led the world in the first phase of the biotechnology revolution.

The US Government has consistently supported biotechnology over the last 15 years with the result that the US is leading the charge in the current phase of the biotechnology revolution. US companies lead the field in innovation, as evidenced by the fact that, of the 150 genetic engineering-based healthcare patents issued in the US in 1995, 122 (81 per cent) were to US companies. Only 11 were to EU companies (source: The US Biotechnology Industry. US Dept. of Commerce - Office of Technology Policy, Washington, Sept. 1997). Luckily, there is too much to be done for the US to do it alone. Ireland is well positioned to play a role consistent with its strong pharmaceutical and food industries, an excellent hospital system and 500 biotechnology graduates (BSc) graduating per year.

1.5.2 The Commercialisation of Biotechnology

Commercialisation of biotechnology was galvanised by the foundation of the first biotechnology company, Genentech, in 1976, in California. The company was started by a small number of mostly American university-based geneticists, a business entrepreneur and venture capital. Since then the growth in the number of biotechnology companies has been remarkable. Many have been small and have failed but they have fuelled the modern biotechnology industry by drawing in huge amounts of venture capital, much of it from

Europe. There were about 200 companies in the US in 1984 (US OTA Report 1984) and few elsewhere. Today, of the estimated 2,300 biotechnology companies world-wide, approximately 1,500 are located in the US. Europe is in second place (with approx. 700 companies), while the Japanese (with approx. 50 companies) are regarded as having been less successful. The biotechnology industry has, from its inception nearly 20 years ago, grown enormously. The current market value of biotechnology companies world-wide is estimated to be in the region of $500 billion (Nature Biotechnology, July 1998) and this does not include the private companies or the major pharmaceutical companies, all of which are now heavily involved with, and dependent on, biotechnology.

Biotechnology gradually took hold in the major pharmaceutical companies and is now causing a massive reorganisation of this sector and also of agribusiness. The emergence of biotechnology has been partly responsible for some remarkable re-structuring of large companies and the amalgamation of others. Major pharmaceutical companies own or part-own one or more free-standing biotechnology companies. For example, Roche owns 60 per cent of Genentech. Many pharmaceutical companies have one or more strategic alliances or contracts with other biotechnology companies. Smith Kline Beecham has signed a contract for $125 million with the genomics company Human Genome Sciences. The restructuring has often involved major strategic changes in company objectives. ICI 'spun off' a separate pharmaceutical company, Zeneca, which has outperformed its parent which continues to concentrate on chemicals. Monsanto began switching from chemicals to agribiotechnology in 1985. Since 1997, Monsanto has invested $6.6 billion in biotechnology. Du Pont is restructuring, putting its energy division Conoco up for sale and buying out Merck's share of a joint biotechnology company for $2.6 billion to *'capitalise on the considerable synergies at the research level in genomics, biology, chemistry and biotechnology'*. Dow Chemicals has announced that it will become a life science company. Hoechst is also divesting itself of parts of its chemical business and moving even more strongly into biotechnology (Enriquez, J. Science 281, (1998) 925 Genomics and the world economy).

In 1982 Schering Plough, the first major pharmaceutical company to develop a biotechnology strategy, spent $60 million on biotechnology. Today the major pharmaceutical companies have biotechnology R&D programmes that typically cost $250-$500 million per year. The research budget of the Chief Scientific Officer of Genzyme, a top level but small biotechnology company, is $150 million.

Extraordinary alliances are being made:

"As health strategies shift from treatment to personalised prevention, agriculture, food and nutrition are also merging with biotech and pharmaceuticals. Genzyme Transgenics is 'pharming' genetically engineered goats. One herd may produce enough antithrombin III to replace a $115 million factory. .... In 1998 Monsanto created a joint venture with Cargill, one of the world's largest private companies (which trades in grain), to process and package genetically engineered foods. .... This is creating a new industrial sector, agriceuticals" (Enriquez, J. Science 281, 925 1998. Genomics and the world economy).

Agriceuticals merges with another novel industry nutriceuticals, in which food is produced as if it is a pharmaceutical. Companies in these interfaces may produce vaccines which are delivered within foods, especially plants. Plants which are vitamin deficient will be genetically engineered to provide important vitamins.

"Future mergers will increasingly take place outside a company's traditional industry" because "today the breadth of complementary technologies is far greater". (Enriquez, J. Science 281, 925 1998. Genomics and the world economy).

In summary, biotechnology has been a major catalyst in stimulating massive changes in multinational industries which have important stakes in the Irish economy. Ireland must prepare for collateral effects.

1.5.3 The US peace dividend - the switch to biotechnology

The cold war is over and biology is in the process of taking up the slack in the defence budgets in the US and to a lesser extent in Europe. The switch is being supported by strong demands in the life sciences sector which can be met in part by the new biotechnology:

- *better health care*
- *healthier life style*
- *ageing*
- *higher food production (for the developing world)*
- *improved food quality*
- *food traceability*
- *safer food*
- *energy efficiency*
- *alternative energy*
- *cleaner chemical production*
- *biodegradable chemicals*
- *care for the environment*
- *conservation*

It is striking that some leading computer scientists and engineers have been quick to see the opportunities and to see them in the time-frame of the process of going from discovery to product via technology and commercialisation. Biology today is where the semiconductor industry and computer science were in the1950s, viewed both in the state of the technology and in the way governments are taking notice.

Ben Rosen, Chairman of the Compaq Computer Company, put it this way:

"A lot of companies I have been involved in have emerged from the explosion of understanding of semiconductors and microprocessors that occurred in the 1950s, '60s and '70s. That technology went rather quickly from a research phase to commercial success. Today, we're at a similar stage where technology is making possible an explosion in knowledge and applications in biology. There's an opportunity through new discoveries and technologies to create wonderful uses for mankind in terms of helping to cure diseases and accelerating other advances. The biological sciences will be the most exciting science and technology of the next few decades" (Caltech News, 32, 2 (1998))

It is very important to understand the strategic significance of this statement. It is a judgement not just about where the science is going (many very big discoveries will be in biology) but also about where the money to pay for the science will come from. Modern industry is essentially based on US and European government investment in science and technology with significant commercial refinements, including some from Japan. In the cold war period the US Government spent a lot of money on defence and some of this, especially contracts at Bell Labs, led to the foundation of the US semiconductor industry, the computer industry and microelectronics. These industries are a collateral of the US Government defence budget. The US peace dividend is being spent on biology.

1.6 National and International Policy outside the United States

The United States had a lead of about 10 years in the first phase of the biotechnology revolution. Europe, Japan and other OECD countries have been trying to catch up by various mechanisms. European multinationals, frustrated with the fragmented and uncertain regulatory framework in Europe, simply bought into the United States. European venture capital has funded much US commercial biotechnology.

The engine of the United States biotechnology industry from 1972 to 1990 was university-based R&D. In Europe, the EU has funded biotechnology in the universities through a series of biotechnology research programmes starting with BEP in 1979. The EU programmes have been effective in building up links between scientists and industries across the EU and European biotechnology now seems to be gathering speed. Recently, several European Governments have recognised the importance of the biotechnology industry in the creation of wealth and jobs and have taken various steps to encourage its development within Europe. The estimated value of products and services using biotechnology in Europe in 1995 was around e40 billion, associated with 300,000/400,000 jobs. The frequently quoted prediction is that products and services using biotechnology in Europe may reach e250 billion by the year 2005 and affect more than three million jobs. This represents a revolution comparable in scale to that of information technology.

Germany is an example of what can be achieved in a short time. Between 1996 and 1998, investments in German biotechnology grew five-fold to $241 million per annum (source: SCRIP, 2340, June 3, 1998). One reason for this rapid growth has been the BioRegio programme, under which the Government provided $360 million in special funding and loans to selected regions of the country to create biotech ‘boomtowns’. This concept has served as a catalyst and contributed to the formation of many biotech start-up companies. Another consequence is the reversal of the German ‘brain-drain’ to the US.

In 1994, the Danish Government decided to initiate a national strategy for research. It has taken several steps in a comprehensive effort to support research and innovation in biotechnology. Most significant is its decision to increase its public research spending considerably with the expectation that science and technology will stimulate the generation of jobs and wealth. The Danish Government increased its spending on biotechnology R&D from $60 million in 1989 to $125 million in 1995 to $160 million in 1998.

Other governmental moves in Europe include the French Federateur pour les Biotechnologies programme, the Swiss Government’s Commission of Technology and Innovation and a virtual organisation, The Flanders Inter University Institute for Biotechnology, linking 700 researchers, which has been set up in Belgium.

In Asia, Japan has a major biotechnology programme and South Korea has been considering major investment programmes.

In an effort to spread the technology into the developing countries the United Nations Industrial Development Organisation established the International Centre for Genetic Engineering and Biotechnology. The Governments of Thailand, Vietnam, Brazil, Kuwait, Egypt and many other developing countries have been made aware of the opportunities for using biotechnology in addressing specific national problems in healthcare and agriculture.

1.7 The impact of the biotechnology revolution

The first phase of the biotechnology revolution has had a remarkable impact. It has caused a huge increase in our knowledge of biology - there is no field of biology, including medicine and agriculture, which has not been fundamentally jolted by the use of biotechnology. Examples are as diverse as the identification of the gene for cystic fibrosis, the discovery of ribozymes and the verification of Kimura's 'Neutral Theory of Molecular Evolution'. There have been extraordinary commercial successes notably in pharmaceuticals, plant breeding and forensic science, and the successes are coming ever more quickly.

The impacts of biotechnology include:

Healthcare

- By 1982 the first major product, human insulin, was on the market. Now there are 60 major biotechnology products. (source: EuropaBio report, 1997).
- Some products, including human insulin and erythropoeitin (EPO), have annual sales of more than £1 billion.
- Other products include the new hepatitis B vaccine, the recombinant Factor VIII, ß-interferon for multiple sclerosis, pulmozyme for cystic fibrosis and the new protein inhibitor drugs against AIDS.
- Biotechnology products comprise a very significant percentage of the products in the pharmaceutical pipeline. Analysts estimate that 16 per cent of all new pharmaceutical products produced have some form of biotechnology associated with their research and development. This figure is expected to rise to 30 per cent after the year 2000 and to 50 per cent by 2010.
- The diagnostics sector is already dominated by biotechnology. There are more than 600 diagnostic products on the market that are based on biotechnology. The sales of the major biotechnology products used (i.e. immuno - or DNA-probe assays) are estimated to be worth e6.3 billion. ('European Biotech '97 - A New Economy' The Fourth Annual Ernst & Young Report on the European Biotechnology Industry)

Food and Agribusiness

- Annual sales of recombinant ag-bio products currently total about e360 million world-wide and are expected to reach over e8.1 billion by 2005. (source: Industry Canada Strategies Database. May 1997)
- Genetically manipulated crops (potatoes, cotton, maize etc.) are being planted on a huge scale in the United States; new varieties are more resistant to pests or can be treated with less and safer pesticides.
- Genetically engineered soybeans will provide 50 percent of Argentina's 1998/99 soybean crop and this figure is expected to rise to 80 per cent by 2000/01. Argentina is the world's third largest soybean producer, after the United States and Brazil.
- Biotechnology products have had a largely unnoticed impact on food processing through the production of industrial enzymes (e.g. chymosin in cheese production).

- The world market for veterinary vaccines now stands at e1.4 billion. Genetically-engineered vaccines presently account for only 3 per cent of sales but this figure is expected to reach 50 per cent within 10 years with a value of e2.7 billion. (source: Industry Canada Strategies Database. May 1997)
- Agriculture, food and nutrition are merging with pharmaceuticals, driven by the common technology of biotechnology.

Forensic Science

- DNA testing is revolutionising forensic science. A single hair root has enough DNA to give a reliable DNA fingerprint.
- The UK data base, which holds DNA profiles of all those previously convicted of violent crimes, is getting large numbers of ‘hits’ with new scene-of-crime samples leading to rapid identification of suspects.

Environmental

- The European market for this industrial sector is estimated to be e1 billion , rising to e11 billion by 2005.(source: EuropaBio report, 1997)
- The world bioremediation market alone is estimated at almost e400 million (source: Industry Canada Strategies Database. May 1997). As pressure for higher EU standards increases, and as legislation is increasingly applied, the environmental industry looks set to steadily grow.

General

- 4,000 biotechnology patent requests for DNA sequences were filed in the US Patent and Trademark Office in 1991. 500,000 DNA sequences were filed in 1996.
- New biotech companies (Millennium, Incyte, Human Genetics Sciences, Genome Therapeutics) are collecting and selling DNA sequence data through massive alliances with large pharmaceutical companies.
- The major pharmaceutical companies have very large in-house DNA sequence programmes and are basing much of their new R&D on genomics, DNA chip technology, combinatorial chemistry and robotics screening programmes.
- The major pharmaceutical companies are trying to hire large numbers of bioinformaticians (Smith Kline Beecham is increasing its staff of bioinformaticians from 2 to 70).
- Denmark spent $150 million on public biotechnology research in 1995, employing 1,450 people in 134 facilities and five basic research centres.
- Building the infrastructure for successful biotechnology is the most important step now, since we want Germany to become a dominant force in biotechnology by 2000’ Ekkehard Warmuth, Head of the German Research Ministry Biotechnology Programme.

1.8 Ireland: a world class player in biotechnology

The new phase of biotechnology has very important implications for Ireland. Ireland was not well placed to take a full part in the early developments of biotechnology. In general, Europe did not get into this phase (largely because the science base was in the US, the regulatory framework in Europe was fragmented and flawed etc.). Some European companies such as

Novo Nordisk, Hoechst and Glaxo, did develop strongly but all had to buy heavily into the United States, setting up or acquiring biotechnology companies there.

The situation is different today. As the biotechnology industry is going through an extraordinarily dynamic reorganisation, Ireland can take advantage of the fluid situation and ensure that it develops a strong biotechnology based industry. Europe is beginning to participate much more strongly and Ireland has the capacity to do so as well.

In spite of some significant weaknesses, Ireland is in a good position to take part in the next phase of the biotechnology revolution. However, it will not be able to participate optimally unless a number of key steps are taken to create a competitive biotechnology infrastructure.

The positive factors are as follows:

- Ireland is pre-eminently a biological economy. Industry related to the health and life sciences (pharmaceuticals, chemicals, medical devices, food etc.) and the unprocessed products of agriculture, fisheries and forestry account for a very large proportion of jobs and exports.
- The major pharmaceutical companies are now lead players in biotechnology. Ireland has a strong pharmaceutical sector. It is primarily a manufacturing industry, comprising 75 companies and employing 11,000 people (1996: IDA). The majority of these pharmaceutical companies are multinationals. Nine of the top ten pharmaceutical firms in the world have manufacturing operations in Ireland. The vast majority of pharmaceutical production is exported. In 1997 pharmaceutical exports were IR£6.22 billion (16 per cent of all exports).
- Ireland has a strong chemical industry comprising about 60 companies and employing approximately 4,000 people. Pharma/chem is the second largest export sector in Ireland after engineering/ electronics and represents about 20 per cent of manufactured goods exported (total exports for the pharma/chem amounted to IR£8,800 million in 1997). The effects of biotechnology can be seen in many ways. For example, chemical companies are using biotechnology to develop novel manufacturing processes. They are developing clean biodegradable biological compounds as substitutes for ‘dirty’ chemicals. Some chemical companies are gradually moving out of the chemical industry altogether and into biotechnology.
- Schering Plough, a world leader in biotechnology, has its major biotechnology protein production plant in Ireland, one of the first in the world.
- Ireland has a major indigenous multinational biotechnology company, Elan. Elan has a strong biotechnology research programme in Ireland.
- There are Irish venture capital funds which are beginning to look at biotechnology.
- There is a small but steady flow of biotechnology start-up companies. Trinity Biotech, is publicly quoted. Biotrin has been funded by venture capital. The Royal College of Surgeons of Ireland has established a new company, Surgen. There are several smaller start-up campus companies, such as Identigen and Optigen.
- IBEC has founded the Irish Bioindustries Association.
- BioResearch Ireland has created a national network of biotechnology.
- Ireland has a large indigenous food processing industry with some of the largest food ingredients companies in the world (Waterford Avonmore, Dairygold, Kerry). The food industry employs 40,000 people (source: Food Drink and Tobacco Federation Annual Review 1997). In 1997, food production accounted for 31 per cent of Ireland’s Gross National Product. There is a very significant drinks industry. Total exports from the food and drink industry amounted to IR£4.1 billion in 1996. Teagasc has significant expertise

in agribiotechnology especially in relation to food processing and classical plant breeding.

- The Irish medical system is excellent, with five medical schools and ten major teaching hospitals with many links to the international pharmaceutical industry.
- The Wellcome Trust, the largest biomedical research trust in the world, funds substantial projects in Ireland.
- Irish universities have about 500 academic staff working in subjects related to biotechnology. There are some very strong Irish biotechnology research groups. For example, the Wellcome Ocular Genetics Unit (P. Humphries, J. Farrar and P. Kenna) at the Smurfit Institute of Genetics, has an international reputation for its research on retinitis pigmentosa. It has had a total research income (1986-98) of IR£6,967,000 (3.3 per cent from the Irish Government, 9.8 per cent from Irish charities and 87 per cent from abroad). Irish scientists have participated successfully in European biotechnology programmes and are well connected to international networks.
- Irish universities are producing about 500 high quality biotechnology graduates per year.
- Many Irish biotechnologists are working abroad in senior positions either in universities or industry.
- The Irish National Centre for Bioinformatics has trained a number of highly qualified bioinformaticians. The Irish IT and microelectronics sector is highly developed and well-positioned to collaborate with biotechnologists.
- There is a regulatory framework for the protection of the environment (EPA), for food safety (FSA) and for the supervision of medical and veterinary medicines (Irish Medicines Board).
- Ireland has a very strong software industry. There are huge synergistic opportunities available to Ireland through combining its expertise in health and life sciences with its expertise in information technology. There is the potential to develop strong information-based bioinformatic companies, which rely on their access to knowledge and their ability to interpret and apply it for their competitive success. In other words, knowledge intensive industries which combine computer science and biology.

The main negative factors are as follows:

- Irish Government science policy has not been consistent, it has been fragmented, it has had short term objectives and it has been poorly funded. After Greece, Ireland has the lowest level of government supported R&D, at less than 1 per cent of total government expenditure (source: Executive summary and highlights of the Second European report on S&T indicators, 1997).
- The combined Irish Government funding of biotechnology through Enterprise Ireland, BioResearch Ireland, the Health Research Board and Teagasc cannot sustain an adequate biotechnology infrastructure.
- The overall structure of the Irish national biotechnology research programme is weak, the output is small, the number of top quality biotechnology research groups is small, those which do exist are not securely funded by Irish money and few can maintain steady lines of investigation for more than a few years. In summary, the number of world class biotechnologists is too small to sustain a biotechnology industry.
- Irish biotechnology graduates are leaving the country in large numbers.
- Irish science students are not encouraged or educated to become STI entrepreneurs.
- Multinationals in Ireland carry out little significant R&D and virtually no basic R&D. The tax environment does not favour multinational R&D.

- There is little funding for start-up companies and little understanding of the scale of investment required.
- Irish venture capital funds have little experience of biotechnology.
- Ireland is not perceived as an international centre of biotechnology.
- The regulatory authorities are not sufficiently well resourced to process applications for product approval as rapidly as agencies in the United States and other European countries.

In summary, the biotechnology infrastructure needs to be strengthened significantly if Ireland is to benefit optimally from the biotechnology revolution in the decades ahead.

The Irish Government has been made aware of the potential of biotechnology for many years. The first reports were drawn up in the early 1980s. Forfás, the State Agency charged with driving Ireland's industrial policy, has again recently identified biotechnology as a key enabling technology for Ireland's future industrial development (source: Shaping Our Future - A Strategy for Enterprise in Ireland in the 21st Century - Forfás 1996). The Irish Biotechnology Industries Association (IBIA) has prepared a position paper 'Biotechnology Industry - a unique opportunity for Ireland to be a World Leader'. According to Enterprise Ireland, the State Agency responsible for indigenous industry, both the healthcare and biotechnology sectors represent significant opportunities for Irish industries to develop (source: Irish Healthcare and Biotechnology Industry - An Emerging Growth Sector - Forbairt).

It is now vitally important that the Government, universities and industry co-operate in reforming the biotechnology infrastructure. We suggest how this can be achieved below.

Maximising Benefits from Biotechnology by 2015

2.1 Strategic Questions
The Health and Life Science Panel has approached the strategies issue by addressing two major questions
• **What infrastructure does Ireland need in order to support and develop a thriving health and life science industry?** • **What areas within biotechnology need to be developed to suustain successful R&D programmes and business enterprises in Ireland?**

2.1 Strategic Questions

What infrastructure does Ireland need in order to support and develop a thriving health and life sciences industry?

Biotechnology industry is highly dependent on research output and research spending is therefore an essential aspect of development of a national biotechnology sector. No country has developed this sector without investment in R&D and no successful national development programme has ever been initiated by any country without addressing this need. Ireland has been a low spender on R&D and this has seriously limited our ability to develop this sector in the past. Any strategic development of the biotechnology sector must therefore address this issue.

A strong biotechnology infrastructure has many benefits. It will:

- provide the technology and expertise from which Irish biotechnology companies will be formed
- provide the basis for many service industries, as biotechnology companies are major users of sub-contracted services
- stimulate multinational companies to put down R&D roots in Ireland
- provide the technology and expertise which indigenous Irish food and other companies require to remain competitive in the face of the rapidly changing technologies in their sectors
- act as a magnet and anchor for international biotechnology companies.

Many of the ingredients needed to construct a world class biotechnology sector are available in Ireland.

The most significant positive elements are:

i. There is a base of multinational healthcare and IT industries and of indigenous food and drink companies which already operate in the markets which will be most dramatically affected by biotechnology. There is therefore market knowledge and sector experience, and a service industry for these companies.

ii. There is a high output of quality graduates in biotechnolog, and in other disciplines used by bio-industries.

iii. There are large numbers of Irish biotechnology graduates in key positions abroad who have shown a willingness to return if conditions and opportunity allow.

iv. The major Irish R&D performers (especially the universities) have shown their quality and capability by their success in (a) winning research contracts in competitive EU Framework Programmes; (b) winning research contracts from, and licensing technology to, international industries; (c) developing technologies on which new biotech start-ups are being formed; and (d) winning major competitive research contracts from the Wellcome Trust, the largest biomedical research trust in the world. This success has been achieved despite the very low R&D public funding currently available.

v. BioResearch Ireland has established an infrastructure to successfully manage the commercialisation of research output from Irish colleges.

These elements are the base on which to create a world class biotechnology infrastructure.

The Health and Life Sciences Panel therefore strongly believes that a biotechnology infrastructure can be created in Ireland, and recommends that it be pursued by a series of related strategic investments, herein referred to as **The Irish National Biotechnology Investment Programme** (see below).

What areas within biotechnology need to be developed to sustain successful R&D programmes and business enterprises in Ireland?

The range of areas in which biotechnology will be applied is immense and it is not unreasonable to claim that it will have an impact on all sectors and on every Irish person within the next few decades. At the moment it is dramatically reshaping the healthcare industries and is beginning to have an even more fundamental effect on food and agribusiness. It is also affecting the environmental industries, the chemical industry, energy generation and criminal detection procedures. Of these, the most immediate areas for strategic investment by Ireland are healthcare and agri-food. However, the central message from this Panel is that biotechnology will have major effects across all sectors of industry, just as micro-electronics has impacted all sectors in the past. It is therefore inappropriate in this report to suggest the specific areas of priority for research. Instead the Panel advises that Ireland should build robust, broad and flexible scientific capabilities which are applicable to different sectors and can be deployed to meet challenges as they arise. The key to this strategy is a high quality, adaptable and innovative scientific work force.

However, the question of establishing structures to ensure that biotechnology can develop in Ireland is of direct relevance to the Panel. The range of measures required is addressed below through the mechanism of a **National Biotechnology Investment Programme**.

The basic principle is to develop, in parallel, a quality research base and a set of bio-industries that will use the technologies, staff and services deriving from this base. This will require funding

and the establishment of some imaginative schemes, to foster an indigenous industry and to attract overseas companies.

2.2 A model biotechnology infrastructure

An obvious strategy is to examine those countries which have developed successful biotech industries and to learn from their experience.

Examples of strong biotechnology infrastructures from which Ireland can borrow ideas include the United States, and several other OECD countries, such as Denmark, which have adopted major aspects of the US model.

Although it is clearly unrealistic to use the US as a direct role model, an examination of the elements which have created a successful US bio-industry sector is useful. In the US, the forces which have favoured the emergence of the biotechnology industry are as follows:

- the major investment by the US Government in biological research through various mechanisms
- the quality of US universities and the pre-eminence of the US in biological research
- the availability of a role model in Silicon Valley for successful technology transfer from universities to companies and the growth of high-tech industry
- the availability of capital at all stages of development through:
    - tax structures in certain States which strongly encourage personal investment in research-based companies
    - a well developed venture capital industry
    - the existence of NASDAQ as a successful exit mechanism for investors
- the existence of major pharmaceutical companies and the interest of such companies in accessing new technologies
- the recognition by local and national authorities of the long term importance of this industry and the development of policy and regulations accordingly
- a regulatory framework which is uniform, transparent and effective.

One clear message is that the core ingredient for success is the technology emerging from the centres of R&D in the US. The other initiatives are there to support the development of this technology as it progresses through relevant development phases within research organisations and industry. Several other countries have copied this model. The Netherlands, Finland and Denmark are EU examples. As noted above, Ireland has all of the ingredients to do the same.

2.3 An Irish biotechnology infrastructure

Realisation of the proposed strategy requires a strong understanding of the above principles of biotechnology policy in government agencies, in industry and in academia. The basic components are already present in all three. In addition, we have developed, in BioResearch Ireland, a mechanism to link these three sectors. The resulting integrated programme will allow Ireland to exploit the knowledge, information and ideas which are contained in these sectors in the interest of sound social and economic development.

The reward is the development of a sector of industry with very significant growth potential, and with a high relevance to our existing mix of healthcare and agri-business. It is also a sector with an excellent ‘fit’ with our graduate output.

In this context it is worth noting the consequences of national failure to develop a biotechnology sector. We are annually producing about 500 graduates in biotechnology disciplines, and a total of about 2,000 in various biomedical and scientific disciplines who are employable within the biotechnology sector. Several EU countries are strongly investing in biotechnology and are likely to require these skills in the short and medium term. According to a 1995 study by Ernst and Young *'..the macro-economic impact of biotech in Europe will result in a 1 per cent per year growth in employee numbers among industries that use biotech. Among the start-ups......staffing levels are expected to rise by 6 per cent a year to the end of the decade'* . In short, biotechnology will be a significant employer in the next few decades, and Ireland has a pool of highly suitable expertise. Without investment, however, it will not have the jobs in Ireland for them. This will create a significant future 'brain-drain' of Irish graduates unless we develop the conditions to keep this resource at home.

The elements of a biotechnology infrastructure in Ireland are:

People

A biotechnology infrastructure cannot be created without a sufficient number (critical mass) of top quality biotechnologists in the universities and industry, and of managers and other professionals in industry. We already have a good base of graduates, but further training (ideally through research) will also be required. In addition, training of entrepreneurs, and of other management staff for bio-industry, must be a component of the biotechnology development programme.

Technology & Expertise

R&D programmes in universities (including hospitals etc.) and industry, and at the interface between them, are essential components of a dynamic biotechnology infrastructure. A productive national biotechnology R&D programme should provide a continuum from basic and applied research to translational and developmental research. Universities typically carry out research at the pre-competitive end of the spectrum (basic and applied), and companies at the other end (translational and developmental). Mature pharmaceutical and biotechnology companies carry out research across the whole spectrum, as do campus companies.

The programme must create a business environment which encourages Irish industry, both indigenous and multinational companies, to carry out R&D in Ireland. It will be necessary to optimise the tax benefits, the regulatory system and the protection of intellectual property.

Linkage

A productive biotechnology infrastructure must have many linkages between universities, business and industry. This can be ensured by the design of the national biotechnology R&D programme and by tax measures. These linkages should ensure that Irish academic discoveries are commercialised and that Irish industry benefits from Irish academic expertise. A successful infrastructure for this is already in place

Start up companies

'The future success of European universities will depend on how they will successed in fostering enterpreneurship as well as scientific knowledge in their students.(Source: Academic and industrial research co-operation in Europe, ESTA, March 1997). Biotechnology start-up companies typically have been founded by collaboration between university scientists, entrepreneurs and venture capital. Many of the initiatives for start-up companies have come from scientists who have taken the role of entrepreneur. A key element in the development of the US biotechnology industry has been the fact that science and business have created partnerships to form the companies that now form the base of the US bio-industry sector.

The Irish Biotechnology Investment Programme might comprise five elements	
There are five sub-programmes:	
Biotechnology R&D Programme	- to provide technology, knowledge and expertise
Biotechnology Translational Programme	- to ensure that the technology, knowledge are commercialised
Biotechnology Start-up Programme	- to assist the start-up of indigenous bio-industries
Biotechnology Inward Investment Programme	- to develop multinational R&D programmes in Ireland
National Conversation on Biotechnology	- to increase public awareness

2.4 Recommendations for Action

An 'Irish National Biotechnology Investment Programme' as outlined above should be established which is designed to build on our existing strength, and address the national deficiencies.

2.4.1 The Irish Biotechnology R&D Programme

As noted earlier, biotechnology is highly dependent on a competitive research base. To compete, Ireland must invest. However, much of the infrastructure, including significant facilities and skills, is already in place. An R&D investment is therefore being made within a reasonably well developed system. A significant programme must be developed to develop a core of R&D activity in Ireland. Separate R&D programmes would be designed for start-up companies and other companies.

The output of this investment will be:

a. a flow of highly qualified, inventive, entrepreneurial biotechnologists

b. a flow of discoveries, technologies and ideas on which products, processes and services can be developed by Irish and Irish-based international industry

c. a level of activity which will raise Ireland's profile in this field, with benefits to all of the other objectives of the programme.

These objectives can only be created through a s*ignificant national biotechnology/bioscience competitive research programme* at peak training 400 research scientists per year for industry.

Such a programme would be designed to carry out 'leading edge' R&D in the biosciences and biotechnology relevant to medicine, industry, agriculture, fisheries, forestry and the environment.

Internationally competitive biotechnology/ bioscience research is carried out by research groups which average 10 people and are led by a principal investigator. A group is funded by a five year lead competitive research grant of IR£300,000 per annum which might be attached to industrial sponsorship or international funding of IR£300,000. There should be 200 such groups in the health and life sciences sector in Ireland. This scale of activity could not be reached immediately. It will take about five years to assemble this number of quality teams during which period the costs will rise from IR£22.5 million in the year 2000 to IR£60 million per annum by about 2004.

The programme might have 100 groups in biomedical science (infectious disease, virology, microbiology, parisitology, heart disease, inflammatory disease, autoimmune disease, neurodegenerative disease, ageing, cancer, genetic disease including obesity and allergies, neuropsychiatric disease, drug addiction, preventative medicine, environmental epidemiology); 60 groups in agribiotech and food biotechnology (vegetables and crops, fish and shellfish, food processing and nutrition, food microbiology and food safety, animal and plant pathogens); 20 groups in IT, bioinformatics, genomics, proteomics, enzymology and drug discovery; 10 groups in environmental regulation, pollution waste disposal, re-cycling and bioenergy production; and 10 groups in instrumentation (DNA chips), biomaterials (e.g. polyhydroxybutyrate) and drug delivery.

Research projects within this R&D programme would be decided on the basis of proposals from researchers which would be assessed by international panels.

For this programme to be effective and produce research output of the standard necessary to contribute to a competitive research and industry base in biotechnology, it is vital that an effective performance evaluation system is put in place. This should be modelled on the US system. Each five year research programme of a laboratory should be stringently assessed by international reviewers at the end of its fourth year. If the reviewers decide it has been productive, their opinions will be influential in deciding whether to continue each programme. Continued funding from central government for a research programme will depend on its success in this process.

2.4.2 The Irish Biotechnology ‘Translational’ Programme

An increased pool of research activity must be matched with an additional focus on the commercialisation of research output, and specifically on developing links between industry and researchers, and on the formation of start-up companies based on the technology. This function is already performed by BioResearch Ireland (BRI) which was established in 1987 as a partnership with the universities. BRI was designed to facilitate generation of ideas and opportunities, and their commercialisation. The universities contribute their facilities and the ideas of their staff, BRI provides funding and innovation management expertise. BRI runs centres within five universities in which research and commercialisation activities are conducted. The activities of all centres are co-ordinated and controlled by a central BRI management team with expertise in patents and licensing, marketing, business development, product management and finance. This team is closely integrated with centre colleagues, and a strong corporate identity has been established within the organisation.

This activity, and other initiatives which result in research outputs or expertise being converted to economic benefit, is an important component of the overall programme.

2.4.3 The Irish Biotechnology Start-Up Programme

Enterprise Ireland should establish the **Irish Biotechnology Start-Up Fund** to invest in biotechnology companies which are in the early stages of development. In particular, it can be expected that some of the technologies arising from the increased R&D activity will need significant seed investment before they can attract conventional venture capital. BioResearch Ireland’s experience has shown that viable technologies, with patent protection and with data to show their validity, still require a phase where company staff are identified, partners found and the company plans developed. This seed-stage requires a funding and management input which is almost entirely absent at the moment. This is an important component of an Irish programme.

The objective should be to support up to 50 biotechnology start-ups in the next 15 years.

Current best estimates are that the amount of seed capital required to fund a biotech start-up is approximately IR£3 million at start-up. Enterprise Ireland has accumulated close to IR£90 million through its own portfolio management. A proportion of this should be channelled back into early phase biotechnology companies.

The possibility of the State reclaiming some of its initial investment in such ventures should also be examined. The eventual aim ought to be to establish a self-perpetuating fund. However, the State will need to make the initial injection of capital into this fund. An investment of IR£30 million per annum for the first three years will establish a self-financing fund. This initial State investment will serve the additional purpose of leveraging venture capital funding.

There are indications that international venture capital might be available to provide matching funds and advise on the management of an Irish Biotechnology Start-Up Fund on the scale envisaged.

2.4.4 Biotechnology Inward Investment Programme

The Irish pharmaceutical industry is a vital national asset. This industry is dominated by multinationals and links Ireland to the international pharmaceutical industry, the leading player in the biotechnology revolution. Nine of the top ten multinational pharmaceutical companies have major manufacturing operations in Ireland. This situation has great significance for the development of biotechnology in Ireland.

A deficiency of the Irish biotechnology system is the relatively small scale of the sector. One of the ways in which we can address this is to promote further activity by existing foreign industry across all functional components of companies including research, technical support and manufacturing. We should also attract further foreign biotechnology enterprises to Ireland.

This will have beneficial effects on the sector similar to those seen in other sectors in the past, i.e. it will train and give experience to Irish graduates, and it will support the development of biotechnology service industries. A few lead companies could have a disproportionately positive effect.

Ireland needs to create an international image as a focus for biotechnology. Attraction of some international biotechnology companies would be a significant advantage. We need to devise a very strong financial and tax package for this purpose.

IDA Ireland should be given a specific remit to market Ireland as a location for biotechnology inward investment. Their target markets should be the USA, UK and Germany. As biotechnology moves from phase 2 and 3 clinical trials to manufacturing, Ireland must exploit its existing expertise in pharmaceutical manufacturing to attract these companies.

2.4.5 The Irish National Conversation on Biotechnology

There is a need to consider ways of dealing with the pressures which are created between public demand for products/processes that enhance the quality of life and public concerns about the long term effects of genetically modified products/processes. There is a potential for conflict between the demand by industry and the research community to move forward and capitalise on the economic opportunities presented by biotechnology and those who advocate a broader perspective that would take into account the long term social/ environmental/ethical/safety impacts of these types of technological developments. It is incumbent on those who work in the field to get involved in a scientific manner in the public debate on the issues. The need to have a communications strategy in biotechnology that uses a partnership approach with ongoing, transparent and open dialogue should be a priority of any initiative. It should aim to increase public awareness and participation, information, communication and confidence.

Conclusion and Follow Up

Scenario 1

If Ireland fails to establish the Irish National Biotechnology Investment Programme

- Irish scientists and technologists with experience in the biomedical sciences, food sciences and biotechnology will emigrate to participate in the major biotechnology R&D programmes abroad and to staff the international biotechnology industry abroad.
- The Irish university teaching and research programmes in biomedical sciences and biotechnology will become outdated and disconnected from those in Europe and the United States.
- The quality of Irish biomedical and biotechnology graduates will decline.
- The multinational pharmaceutical and chemical industries will not be able to find sufficient numbers of qualified Irish biotechnology graduates.
- The pharmaceutical and chemical industries in Ireland will not have established the R&D programmes in Ireland which would have acted as an anchor to keep these companies in Ireland.
- Few Irish biotechnology companies will be started or mature.
- Existing Irish biotechnology companies may move abroad.
- No multinational biotechnology companies will set up manufacturing operations or R&D laboratories in Ireland.
- Irish venture capital will be invested in European and American biotechnology companies.
- Irish agriculture will not maximise the benefits of the introduction of more efficient, more diversified ‘green’ crops.
- Irish agriculture will not participate significantly in the production of novel products from plants (e.g. plastics, pharmaceuticals, hormones, vaccines, and vitamins and other specific nutrients).
- The Irish food industry which specialises to some extent in bulk ingredients will be slower to adapt to the production of speciality food ingredients from new sources.
- Large players in the Irish food industry may be taken over and become dependent on foreign R&D.

Scenario 2

If Ireland establishes the Irish National Biotechnology Investment Programme

- Ireland will have a much more powerful, stable, robust, innovative, health and life sciences industry strongly dependent on Irish brain-power.
- The expanded and secure health and life sciences industry will include spin-off companies derived from food and pharmaceutical companies, IT and microelectronics companies, medical devices companies, and chemical companies, already located in Ireland.
- New biotechnology companies with strong R&D programmes will have been set up by inward investment.

- Indigenous start-ups based partly on Irish discoveries will be facilitated.
- There will be a significant increase in the number of employees in the biotechnology industry.
- There will be a more diversified agricultural sector which will grow plants for the chemical, pharmaceutical and food industries.
- There will be a more innovative food and drinks industry allied to international pharmaceutical companies.
- There will be a highly efficient regulatory system and strong public approval for biotechnology projects.
- There will be a strong service sector providing support systems for the biotechnology industry.
- Ireland will be recognised as a biotechnology cluster

Follow up

The objective is to have the **Irish National Biotechnology Investment Programme** included in the budget for the year 2000.

As a start to this process, the Irish Council for Science, Technology and Innovation (ICSTI) should ask Forfás to organise an Irish Biotechnology Forum at which the Health and Life Sciences Panel would discuss this document with the Minister for Science and Technology and senior officials from the relevant Government Departments. The seminar should be addressed by a select group of biotechnology industry leaders, including some whose companies have manufacturing plants in Ireland.

Appendix I Panel Members

Professor David McConnell, Chairman	Genetics TCD
Dr. Mike Comer, Deputy Chairman	Caramed Ltd
Dr. Brian Brady	Schering Plough (Avondale Company)
Dr. Gerry Byrne	Jacobs International
Professor Martin Clynesr	National Cell & Tissue Culture Centre, DCU
Dr. Margaret Creedon	Abbott Laboratories
Noel Crimin	Organon Teknika
Dr. Dan Donnelly	Guinness Ireland Group Ltd - Diageo
Dr. Liam Donnelly	Teagasc
Dr. Jane Farrar	Genetics Department, TCD
Dr. Desmond Fitzgerald	Royal College of Surgeons Ireland
Professor Tim Foster	Microbiology Department, TCD
Dr. Ann Francis	Quest International Ireland Ltd
Dr. Frank Hallinan	Irish Medicines Board
Denis Hayes	Avonmore Waterford Group plc
Dr. Tony Kavanagh	Genetics Department, TCD
Dr. Cormac Kilty	Biotrin Holdings
Pat MacGovern	IDA Ireland
Dr. Barry McCleary	Megazyme International Ireland Ltd
Matt Moran	IBEC
Dr. Dan O'Mahony	Elan Corporation
Dr. Luke O'Neill	Biochemistry Department, TCD
Dr. Patrick O'Reilly	Monsanto
Dr. Thomas Quigley	Food Safety Authority of Ireland
Dr. Mark Rogers	Zoology Department, NUI - Dublin
Dr. Douwe van Sinderen	Microbiology Department, NUI - Cork
Dr. Owen Smith	St. James's Hospital, National Childrens' Hospital
Professor Brian Walker	Biochemistry Department, QUB
Dr. Patrick Wall	Food Safety Authority of Ireland
Dr. Jim Walsh	Trinity Biotech
Professor Philip Walton	Physics Department, NUI - Galway
Dr. Fiona Shalloe, Secretary	National Pharmaceutical Biotechnology Centre, TCD

Appendix II Steering Committee

Prof. DavidMcConnell
Dr. Mike Comer
Mr. Matt Moran
Dr. Jim Ryan
Prof. Brian Walker

Appendix III Some Key Technologies and Research Themes

Some Key Technologies and Research Themes

[Sources: Dr. Peter Daly's Report to the Technology Foresight Health & Life Sciences Panel, October, 1998; Prof. Phillip Walton, personnel communication; Dr. Dan O'Mahony, personnel communication]

Technologies

1. Genomics

There are over 100,000 genes in the human body. The Human Genome Project aims to fully sequence all of these by the early years of the next century. Meanwhile biotechnology companies involved in genomics have established major proprietary databases of EST (expressed sequence tags) for a large proportion of human genes and are using these in association with positional cloning strategies. ESTs are created by partially sequencing randomly chosen gene transcripts that have been converted into cDNA. This is a simple but enormously powerful tool from which to probe or monitor every gene. Prior to 1990 only 1,000 genes had been identified in the human genome. Within a few years EST technology increased that number by almost two orders of magnitude. Many companies have created vast relational databases of EST derived information including sequence, homology, functional annotation and gene expression data. Positional cloning aims to identify genes which are associated with diseases in human tissues as novel targets and has led to the identification of a range of important genes. discovery efforts will have to commence with consideration of the genetic data available from these programmes. [1]

2. Functional Genomics

Although vast libraries of EST data and full length sequence data are available, only a tiny fraction of the genes are known as to their function. The area of functional genomics aims to identify gene function with the objective of identifying novel targets for drug discovery. Functional genomics involves a number of different fields. As well as the Human Genome project, the full genome of a number of microbes has been fully elucidated. As genes from a number of organisms are highly conserved across evolution, the study of these simpler organisms can result in gene identification and the corresponding gene in humans can then be identified. Gene function can also be studied in human cells using various genetic approaches to identify function. The process of function identification has emerged as a major bottleneck in genomics research and there is likely to be an effort to apply here the same types of automation which are used in gene expression.

3. Gene Chip Technology

A key technology for genomics R&D is the recent development of gene chips. The gene chip is a technology which permits the automation of differential gene expression. Differential gene expression between normal and diseased cells is a key technique aimed at identifying key disease genes. The gene chips are plastic or glass arrays onto which large numbers of cDNA fragments have been spotted at particular addresses. Hybridising cDNA or mRNA from the cells in question allows identification of which genes are 'switched on' through hybridisation on the chip. One product, for instance, contains 27,000 human genes. This is a very powerful technology which will have a major impact on many areas of biological research including the study of diseases and drug discovery. It is also likely to have a major impact on diagnostics. It is likely that future routine diagnostic tests on patients will, through this technology, be able to produce a read-out of the expression levels of the patients' genes and rapidly identify aberrant expression levels or aberrant tissue expression.

4. Bioinformatics

Bioinformatics is a science of recent creation that uses biological data and knowledge stored in computer databases, complemented by computational methods to derive new knowledge. There are a range of major public databases containing gene sequence data and others with protein sequence data. When a novel gene sequence is discovered, rapid progress on identifying its function can often be made by comparing it for similarity (homology) to other sequences in the databases whose function is known. This approach is becoming a major discovery tool. Companies involved in this area use public databases but also have their own proprietary databases such as the EST databases of companies such as Human Genome Sciences and there are also databases containing the complete genomes of a number of micro-organisms. The study of comparative genomes between species is rapidly advancing and is expected to be very useful in function studies. Special software has been developed for these homology searches and we can expect ongoing innovations in this. [2]

5. Transgenic / Knockouts

The ability to generate knockout mouse models has improved greatly over the past couple of years and the service is now available commercially so that one can start with a gene and end up with a knockout animal. The ability to achieve tissue specific knockouts is also very important. However, despite the above, the process is technically difficult and normally takes about one year to achieve. This time problem, combined with its cost, means that it cannot yet become a mass screening system for gene functional analysis. There is an urgent need here for a rapid high-throughput system combined with rapid phenotype analysis. This is a very important area of R&D and any research group or company which can improve on current capabilities would have a very commercial proposition. Related to this are recent advances in cloning especially in producing second and third generation mouse clones. These are likely to be of considerable interest for pre-clinical research.

6. Chemistry methodologies

As with traditional drug design, combinatorial chemistry relies on organic synthesis. The difference is the scope - instead of synthesising a single compound, combinatorial chemistry exploits automation and miniaturisation to synthesise large libraries of compounds. Combinatorial libraries are created by one of two methods: split synthesis or parallel synthesis. In split synthesis or 'split and pool', compounds are assembled on the surface of microparticles or beads. In each step, beads from previous steps are partitioned into several groups and a new building block is added. The different groups of beads are then recombined and separated once again to form new groups; the next building block is added and the process continues until the desired combinatorial library has been assembled. Combinatorial libraries can also be made by parallel synthesis in which different compounds are separated in different vessels without remixing, often in an automated fashion. Split synthesis is used to produce small quantities of a relatively large number of compounds, whereas parallel synthesis yields larger quantities of a relatively small number of compounds. These technologies are used for lead identification in screening and lead optimisation. While huge progress has been made there are still major opportunities to develop this technology further; these include such areas as new linkage methods, the creation of highly diverse universal libraries, the development of new assays and methods, the integration of combinatorial chemistry with structure based design and probably most importantly the further integration of combinatorial methods with functional genomics and proteomics. [3,4,5]

7. Screening & Screen Development

Screening assays in use today use recombinant cellular assays in microbial or yeast cells. The target protein is expressed inside or on the surface of a cell and binding of the ligand to the receptor results in intracellular changes which can be detected by use of a reporter gene construct. For instance use of a luminescence gene will give luminescence on binding of ligands. Other techniques in yeast can be used to analyse biochemical pathways and determine protein-protein interaction. These techniques are a key link in the discovery process between the identification of a target and its protein and the use of combinatorial libraries to screen against. We can expect on-going innovation in the development of screens. It is likely that there will also be major developments in the use of mammalian cells as assays as these are slow and costly to operate today. [6,7,8]

8. IT/Biotech Convergence

The impact of robotics on drug discovery R&D has been very significant over the past few years allowing the development of high-throughput screening systems to match the flood of new chemical diversity emerging from combinatorial chemistry. Whereas a few years ago compounds were tested in 96 well microtitre plates, today mixtures of compounds are tested in 384 up to 864 well plates. This process of miniaturisation is only at an early stage and R&D is currently well advanced to develop a 'lab on a chip' which would use extremely small quantities of compounds for testing. It is likely that a significant amount of compound testing as well as molecular biology and cell biology techniques will be automated and miniaturised over the next decade and this will give rise to a new type of technology which will combine elements of IT with chemistry and molecular biology.

9. Proteomics

Proteomics is the study of the sequence, function and control of expression of the total number of proteins made by an organism. It is the name given to a renewed interest in proteins rather than genes and the link to diseases. Proteomics uses a combination of 2 D gel electrophoresis and high-throughput screening. However there are many difficulties in resolution and automation of this area of R&D. There are many times more proteins than genes due to variations in post translational modification and other factors and this makes the problem a huge one. The use of mass spectrometry combined with chromatographic separation may provide a way forward. Although this is a young field, it may have major long term potential and importance.

10. New Diagnostic Technologies

Increasingly diagnostics will be influenced by the information and technologies emerging from the area of genomics. Molecular biology has already had a significant impact for instance in the widespread use of PCR in diagnostic and forensics. This trend towards gene based diagnostics is likely to expand due to a number of factors; the identification of genes with predictive use in disease prognosis; the identification of disease susceptibility genes; the development of pharmacogenomics and consequent ability to diagnose drug suitability to patient sub-populations and the development of novel technologies such as gene chip technology. These trends may ultimately result in rapid gene analysis technology being available to general physicians which would have major consequences for the way in which the clinical diagnostics market operates today.

11. Biosensors

Biosensors are devices in which a biological component, giving specificity, is coupled with a physical detection technique to produce an electronic signal. Biological components include antibodies, enzymes, nucleic acids, receptors and cells and the physical component includes optical fibers, piezoelectric crystals and electrodes for electrochemical devices. While work has been underway for about forty years only one biosensor of note, the home measurement of glucose by diabetics, has succeeded commercially with sales of about $100 million per year. There are many difficulties to be overcome before other biosensors reach the market. Problems include those of sensitivity, stability, selectivity, quality control and difficult manufacturing techniques. It is still believed that certain niche markets will develop for these devices e.g. in the doctor's office they will compete with central labs where rapid turn around is needed so long as simplicity and low cost can be achieved. Many problems need yet to be solved before the promise of biosensors becomes reality.

12. Drug Delivery

Many patients are required to administer regular or daily injection(s) of drugs for therapeutic reasons. These include drugs such as insulin for treatment of diabetes and growth hormone for growth stature defects in children and adults. In addition, cancer patients are required to administer, on a frequent basis, drugs such as morphine to relieve pain, usually using an external pump system.

The development of alternative drug delivery technologies which make it easier for patients to take drugs (such as peptide and protein based drugs like EPO, growth hormone, insulin, interferons, heparin etc.) by the oral route in tablet or capsule form, will have a number of important benefits both to patients, to the length of hospital stays required by patients, to administrative costs, to nursing need requirements, to the exchequer and to society in general. This applies to all patient populations including the paediatric, the young, the elderly and adult population. In addition, developing such innovative technologies in Ireland will result in high-tech manufacturing employment, product production employment and process improvement employment, again benefiting the economy and the exchequer.

Major Research Themes

1. Gene Function in Disease

The basis of all disease is ultimately genetic and the starting point for most future drug programmes will be the gene. Major programmes today are directed towards identifying genes which play key roles in diseases such as heart disease, asthma, diabetes, obesity, inflammatory diseases etc. Many drugs on the market today do not represent adequate therapy and are not targeted far back enough in the biochemical pathway causing the disease. For instance, many inflammatory and anti-arthritic drugs are unsatisfactory and have unpleasant side effects; in the cardiovascular area, the underlying genetic causes of atherosclerosis, hypertension, CHD and other causes are poorly understood; key events at the gene level underlying cancer development and its interaction with the immune system are poorly understood; diabetes (Type II) is often inadequately treated with current medications and leads to complications and organ damage. It is likely that improved medicines will be discovered across the therapeutic category spectrum over the next decade from the combination of technologies described above.

2. Gene Transcription Factors

The regulation of genes in higher organisms in different tissues and in different conditions is a major challenge which is expected to lead to the identification of many novel targets. Gene expression is controlled, by among other things, transcription factors and a number of companies are working on these. For example, the transcription factor NF-kB activates a range of genes involved in the inflammatory response and Signal Pharmaceuticals Inc. is studying this with a view to developing novel ways of interfering with gene activation in inflammatory diseases. The identification of novel transcription factors and the pathways in which they operate holds considerable promise because it represents a way of short-circuiting an orchestrated genetic response seen in disease processes. [9]

3. Apoptosis

Cell biology has undergone a revolution in recent years with the emergence of new and important research themes such as apoptosis and proliferation research. Apoptosis is a form of natural cell suicide which occurs continuously in the body. Disregulation of this is involved in cancer or a range of other diseases. For instance, cancer cells often are resistant to chemotherapeutic drugs which induce apoptosis and the objective here is to develop therapy to induce apoptosis. In other diseases there is too much apoptosis and the objective is to prevent cell death. There have also been developments in the understanding of cell cycle regulation which are also important for anti-cancer research.

4. Signal Transduction

Signal transduction is the study of intracellular signalling pathways and intracellular receptors. A number of major intracellular signalling pathways have been elucidated and a range of intracellular receptors have been discovered by companies such as Ligand Pharmaceuticals. A number of existing drugs already act inside the cell rather than on its surface such as cyclosporine for immunosuppression or oestrogen for osteoporosis but these were discovered without knowledge of their intracellular effects. The objective of research in this area is to develop novel drugs designed specifically to act inside the cell and to modulate intracellular pathways. One potential problem here is likely to be getting compounds through the cell membrane. However, this area is likely to be very important in the next century.

5. Gene Therapy and Antisense Therapy

Gene therapy involves the introduction of genes into human tissues in order to correct aberrant gene expression or compensate for loss of gene function. Such products are currently in clinical trials and one of the most promising technologies is that of Onyx Pharmaceuticals in which an adenovirus has been constructed which replicates in and kills only cells in which the p53 gene is mutated. This holds considerable promise for cancer therapy. Other companies are developing applications for cardiovascular and other diseases. Gene therapy, however, faces a number of important problems such as the immune response induced by the virus carrying the gene and the problem of getting enough of the gene into and expressed in cells. Antisense technology involves the attempt to selectively block a specific gene by introducing a complementary nucleic acid which will hybridise and block its expression. Although the first antisense product for Crohn's disease has received approval (Isis Pharmaceuticals) this area of R&D has encountered many problems in terms of specificity. If these could be overcome the ability to selectively block gene expression would be of great value therapeutically.

6. Developmental Biology

Developmental biology has emerged as a very promising new field. This area of research aims to identify the mechanisms underlying embryonic development of tissues and organs and specifically genes which are involved in promoting differentiation and growth of different tissue types and in controlling organ development. Companies involved here include relatively new companies such as Progenitor, Ontogeny and Hexagen as well as more established companies such as Amgen and Genentech. A number of major pharmaceutical companies are also involved in R&D here. The potential is the regeneration of tissue which has been lost due to disease by activating genes responsible for growth and differentiation. This is an important area and will receive a lot of research funding over the next decade.

7. Immunotherapy

Immunotherapy seeks to use antigens present on cancer cells to alert the immune system to mount a full scale attack. No such products are yet available on the market. The initial attempts involved using killed whole cells in a manner analogous to viral vaccines and one such product (from Ribi ImmunoChem Research) has completed pivotal clinical trails and is awaiting review by regulatory authorities. The whole cell approach however has a number of drawbacks and alternative approaches are underway in a number of other companies. Much research is now focused on cancer specific antigens and on their presentation to the immune system that elicits a strong response. There is a range of companies with immunotherapy products in development including Antigenics which has a product involving a purified antigen bound to heat shock proteins which is Phase 1 for melanoma, pancreatic and renal carcinoma, Progenics has its GMK vaccine against the ganglioside GM2, to treat melanoma, in Phase III trials and has another related product for multiple cancer types. Biomira has a peptide mimic of a cancer antigen MUC entering clinical trials at the end of 1998 for non small cell lung cancer. This is an important ongoing area of research and the relationship between cancer antigens and the immunological response is an area on which a great deal of further research will be required over the next decade.

8. Microbial Genetics

The resurgence of antibiotic resistance pathogens has focused attention in recent years on a therapeutic area in which it was assumed most problems had been solved namely, infectious diseases. There are now major R&D programmes in many of the pharmaceutical majors addressing the issue of identifying novel targets for improved antibiotics and number of specialist biotechnology companies such as Microcide Pharmaceuticals and Cubist Pharmaceuticals are active in the field. Bioinformatics should assist here in the identification of targets. Suitable targets are those which are essential for survival of the pathogen but are not present in other microbial species. This will be an ongoing R&D programme for a long time. Micro-organisms have adapted successfully over 2-3 billion years; it was a mistake to consider we had beaten them after a few decades of antibiotics.

9. FreeRadical Biology

The discovery of the signalling role of nitric oxide in the 1980s recently resulted in the award of Nobel prizes. Significant R&D efforts are underway in relation to exploiting these discoveries commercially in a number of therapeutic categories. A related field is the area of oxygen free radicals. These also have key signalling functions in relation to gene activation and oxidative stress plays an important role in a number of major diseases. This is likely to become a more significant area of research in future years as more information develops concerning gene control. A related area to this is what might be termed bio-inorganic chemistry and is concerned with the role of metals and metal complexes in biochemical modulation.

10. Plant Biotechnology

The current controversies over plant biotechnology obscure the major long term benefits to human healthcare which are likely from this technology. The engineering of pesticide or pest resistance into edible plants is merely the beginning of a more fundamental transformation involving the emergence of links between food and medicine. In the longer term it is likely that plants will be modified so as to upregulate the production of beneficial phytochemicals which have a protective effect against cancer and various other diseases. The study of the complex phytochemicals, antioxidants etc. which are contained in vegetables such as broccoli, their genetic regulation and structure/function relationships is likely to become a growing area of research over the next decade.

11. Pharmacogenomics

People differ in their responses to drugs and this reflects genetic differences. Pharmacogenomics is the study of these genetic differences with the aim of generating medicines more tailored to an individual's genetic make-up. Differences in drug effects may result from differences in metabolic enzymes, from different disease pathways presenting the same symptoms and from drug effects on other biological pathways. It is not clear that the pharmaceutical industry will embrace this; companies would much prefer one drug with sales of $1billion to 5 variants each selling $200 million. However one advantage for drug companies would be in faster and less costly clinical trials as patient groups could be selected genetically to give good results. A leading company in this area is the French company Genset which is involved in a therapeutic and diagnostics alliance with Abbott.

12. Tissue Engineering

Tissue engineering involves the development of artificial tissues and the stimulation of tissue growth. Companies such as Advanced Tissue Sciences in the US have developed artificial skin and this company also has a product for diabetic foot ulcers. Other approaches involve R&D directed at re-growth of diseased tissue. For example, Collateral Therapeutics is developing gene therapy based product which contains an antigenic growth factor. This is proposed to be used to re-grow coronary arteries in coronary heart disease through a local administration system and could potentially do away with the need for by-pass surgery or angioplasty. Other companies are working on factors which may lead to replacement of lost bone and be useful in treating periodontal and other diseases. It is too early to assess whether these therapeutic approaches will work but it seems an exciting area.

13. Therapeutic Antibodies

Tissue engineering involves the development of artificial tissues and the stimulation of tissue growth. Companies such as Advanced Tissue Sciences in the US have developed artificial skin and this company also has a product for diabetic foot ulcers. Other approaches involve R&D directed at re-growth of diseased tissue. For example, Collateral Therapeutics is developing gene therapy based product which contains an antigenic growth factor. This is proposed to be used to re-grow coronary arteries in coronary heart disease through a local administration system and could potentially do away with the need for by-pass surgery or angioplasty. Other companies are working on

factors which may lead to replacement of lost bone and be useful in treating periodontal and other diseases. It is too early to assess whether these therapeutic approaches will work but it seems an exciting area.

13. Therapeutic Antibodies

The initial promise of monoclonal antibodies as therapeutic agents, especially for cancer, was not realised due to a number of factors including human immunological reactions to mouse antibodies and the size of the antibody molecules and consequent ineffectiveness of the administered antibodies. This resulted in an alternative approach of producing ' humanised ' antibodies and antibody fragments. This R&D has resulted in a number of important new drugs some of which are on the market while a range of others are in various stages of clinical trials. Important new drugs here include ReoPro from Centocor which is used to prevent complications of angioplasty and Ramacide which has been approved in the US in Aug 1998 for the treatment of fistulas associated with Crohn's disease. This is an area of biotechnology R&D which has been slow to live up to its promise but we can expect that it will lead to an increasing number of successful new product launches over the next decade.

14. Neurobiology

Modern molecular biology and cell biology methods have been used for the past two decades in neurobiological research in association with older methods but when this is combined with novel technologies such as genomics and differential gene expression methods we can expect to see major progress. This research may provide new therapeutics for brain injury and neurodegenerative diseases as well as an understanding of learning, memory and other cognitive functions which may also have practical applications. Major research themes here include such areas as neuronal development and differentiation, the role of neurotrophic factors, the role of neurotransmitters and receptors in cognition and disease, neuroendocrine mechanisms in obesity and other areas, positional cloning of genes associated with disease, the molecular basis of neuronal ageing and signal transduction and the connection to neurotransmitter function.

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Appendix IV Meetings

1. Full Panel meeting	22 May - TCD
2. Full Panel meeting	12 June - Food Safety Authority
3. Seminar - 'Biotechnology in Denmark' *Prof. Borge Diderichsen - Novo Nordisk*	24 July - TCD
4. Medical Sub-Panel meeting	14 Sept - IBEC
5. Seminar - 'The Future of Biotechnology' *Dr Alan Smith - GENZYME*	22 Sept - TCD
6. Uncertainties/Scenarios sub-panel	25 Sept - TCD
7. Seminar - 'A Strategy for Irish Biotechnology' *Dr Maurice Treacy - ARIAD Pharmaceuticals*	16 Oct - TCD
8. Full Panel meeting	30 Oct - TCD
9. Seminar: 'Can Ireland Build a Successful Long Term Commercial Strategy for Biotechnology in a Competitive Global Economy' *Dr. Fintan Walton - PharmaVentures*	23 Nov - TCD