
Medical biotechnology: Achievements, prospects and perceptions

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Introduction: Biotechnology, bio-industry and bio-economy

The word “biotechnology” was coined in 1919 by Karl Ereky, a Hungarian engineer, to refer to methods and techniques that allow the production of substances from raw materials with the aid of living organisms. A standard definition of biotechnology was reached in the Convention on Biological Diversity (1992) – “any technological application that uses biological systems, living organisms or derivatives thereof, to make or modify products and processes for specific use”. This definition was agreed by 168 member nations, and also accepted by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).

Biotechnologies therefore comprise a collection of techniques or processes using living organisms or their units to develop added-value products and services. When applied on industrial and commercial scales, biotechnologies give rise to bio-industries. Conventional biotechnologies include plant and animal breeding and the use of micro-organisms and enzymes in fermentations and the preparation and preservation of products, as well as in the control of pests (e.g. integrated pest control). More advanced biotechnologies mainly relate to the use of recombinant deoxyribonucleic acid (DNA) techniques (i.e. the identification, splicing and transfer of genes from one organism to another), which are now supported by research on genetic information (genomics). This distinction is merely a convenience, because modern techniques are used to improve conventional methods; for example, recombinant enzymes and genetic markers are employed to improve fermentations and plant and animal

breeding. It is, however, true that the wide range of biotechnologies, from the simplest to the most sophisticated, allows each country to select those that suit its needs and development priorities, and by doing so even reach a level of excellence (for example, developing countries that have used *in vitro* micro-propagation and plant-tissue cultures to become world-leading exporters of flowers and commodities).

The potential of biotechnology to contribute to increasing agricultural, food and feed production, improving human and animal health, mitigating pollution and protecting the environment was acknowledged in *Agenda 21* – the work programme adopted by the 1992 United Nations Conference on Environment and Development in Rio de Janeiro. In 2001, the *Human Development Report* considered biotechnology to be the means to tackle major health challenges in poor countries, such as infectious diseases (tuberculosis), malaria and HIV/AIDS, and an adequate tool to aid the development of the regions left behind by the “green revolution”; these are home to more than half the world’s poorest populations, who depend on agriculture, agroforestry and livestock husbandry. New and more effective vaccines, drugs and diagnostic tools, as well as more food and feed of high nutritional value, will be needed to meet the expanding needs of the world’s populations.

Biotechnology and bio-industry are becoming an integral part of the knowledge-based economy, because they are closely associated with progress in the life sciences and in the applied sciences and technologies linked to them. A new model of economic activity is being ushered in – the bio-economy – in which new types of enterprise are created and old industries are revitalized. The bio-economy is defined as including all industries, economic activities and interests organized around living systems. The bio-economy can be divided into two primary industry segments: the bio-resource industries, which directly exploit biotic resources – crop production, horticulture, forestry, livestock and poultry, aquaculture and fisheries; and related industries that have large stakes as either suppliers to or customers of the bio-resource sector – agrochemicals and seeds, biotechnologies and bio-industry, energy, food and fibre processing and retailing, pharmaceuticals and health care, banking and insurance. All these industries are closely associated with the economic impact of human-induced change to biological systems (Graff and Newcomb, 2003).

The potential of this bio-economy to spur economic growth and create wealth by enhancing industrial productivity is unprecedented. It is therefore no surprise that high-income and technologically advanced countries have made huge investments in research and development (R&D) in the life sciences, biotechnology and bio-industry. In 2001, bio-industries were estimated to have generated US\$34.8 billion in revenues worldwide and

to employ about 190,000 people in publicly traded firms. These are impressive results given that, in 1992, bio-industries were estimated to have generated US\$8.1 billion and employed fewer than 100,000 persons.

The main beneficiaries of the current “biotechnology revolution” and the resulting bio-industries are largely the industrialized and technologically advanced countries, i.e. those that enjoy a large investment of their domestic product in R&D and technological innovation. Thus, the United States, Canada and Europe account for about 97 per cent of the global biotechnology revenues, 96 per cent of persons employed in biotechnology ventures and 88 per cent of all biotechnology firms. Ensuring that those who need biotechnology have access to it therefore remains a major challenge. Similarly, creating an environment conducive to the acquisition, adaptation and diffusion of biotechnology in developing countries is another great challenge. However, a number of developing countries are increasingly using biotechnology and have created a successful bio-industry, at the same time increasing their investments in R&D in the life sciences.

According to the Frost & Sullivan Chemicals Group in the United Kingdom, some 4,300 biotechnology companies were active globally in 2003: 1,850 (43 per cent) in North America; 1,875 (43 per cent) in Europe; 380 (9 per cent) in Asia; and 200 (5 per cent) in Australia. These companies cover the gamut from pure R&D participants to integrated manufacturers to contract manufacturing organizations (CMOs). The United States has the largest number of registered biotechnology companies in the world (318), followed by Europe (102). In 2002, the annual turnover of these companies was US\$33.0 billion in the United States and only US\$12.8 billion in Europe. Some US\$20.5 billion was allocated to research in the United States, compared with US\$7.6 billion in Europe (Adhikari, 2004).

US biotechnology and bio-industry

The consultancy firm Ernst & Young distinguishes between US companies that produce medicines and the others. The former include pioneers such as Amgen, Inc., Genentech, Inc., Genzyme Corporation, Chiron Corporation and Biogen, Inc. The annual turnover of these five companies represents one-third of the sector’s total (US\$11.6 billion out of US\$33.0 billion); in addition, their product portfolio enables them to compete with the big pharmaceutical groups in terms of turnover and stock value. For instance, Amgen, with US\$75 billion market capitalization, is more important than Eli Lilly & Co., and Genentech’s market capitalization is twice that of Bayer AG (Mamou, 2004e).

In 2002, Amgen, had six products on the market producing global revenues of US\$4,991 million. Genentech was in second place with 11 products on the market and revenues worth US\$2,164 million. The remaining places in the top five were filled by Serono SA (six products, US\$1,423 million), Biogen (two products, US\$1,034 million) and Genzyme Corporation (five products, US\$858 million) (Adhikari, 2004).

Over the past decade, a clutch of companies has amassed significant profits from a relatively limited portfolio of drugs. There is, today, heightened recognition that lucrative opportunities await companies that can develop even a single life-saving biotechnology drug. For instance, Amgen's revenues increased by over 40 per cent between 2001 and 2002 owing to the US\$2 billion it made in 2002 from sales of Epogen and the US\$1.5 billion earned from sales of Neupogen. Over US\$1 billion in sales of Rituxan – a monoclonal antibody against cancer – in 2002 helped Genentech record a 25 per cent growth over its 2001 performance (Adhikari, 2004).

In California, there are two biotechnology “clusters” of global importance: one in San Diego–La Jolla, south of Los Angeles, and the other in the Bay Area, near San Francisco. A cluster is defined as a group of enterprises and institutions in a particular sector of knowledge that are geographically close to each other and networked through all kinds of links, starting with those concerning clients and suppliers. In neither biotechnology cluster does it take more than 10 minutes to travel from one company to another. The San Diego cluster is supported in all aspects of its functioning, including lobbying politicians and the various actors in the bio-economy, by Biocom – a powerful association of 450 enterprises, including about 400 in biotechnology, in the San Diego region. The cluster relies on the density and frequency of exchanges between industry managers and university research centres. For instance, one of its objectives is to shorten the average time needed to set up a licensing contract between a university and a biotechnology company; it generally takes 10 months to establish such a contract, which is considered too long, so the cluster association is bringing together all the stakeholders to discuss this matter and come to a rapid conclusion (Mamou, 2004e).

The clusters have developed the proof of concept, to show that from an idea, a theory or a concept there could emerge a business model and eventually a blockbuster drug. Such an endeavour between the researchers and bio-industry would lead to licensing agreements that rewarded the discovery work. A strategic alliance between politics, basic research and the pharmaceutical industry (whether biotechnological or not) within the cluster would be meaningless without capital. In fact, bio-industries' success is above all associated with an efficient capital market, according to David Pyott, chief executive officer of Allergan,

the world leader in ophthalmic products and the unique owner of Botox – a product used in cosmetic surgery and the main source of the company's wealth. No cluster can exist without a dense network of investors, business angels, venture capitalists and bankers, ready to get involved in the setting up of companies (Mamou, 2004e).

The two Californian clusters represented 25.6 per cent of US companies in 2001. The corresponding figures for other states were as follows: Massachusetts, 8.6 per cent; Maryland, 7.7 per cent; New Jersey, 5.9 per cent; North Carolina, 5.8 per cent; Pennsylvania, 4.6 per cent; Texas, 3.4 per cent; Washington, 3.1 per cent; New York, 3.1 per cent; Wisconsin, 2.5 per cent; the rest of the country accounted for the remaining 29.7 per cent (data from the US Department of Commerce Technology Administration and Bureau of Industry and Security).

Europe's biotechnology and bio-industry

The European bio-industry is less mature than its US counterpart. Actelion of Switzerland qualified as the world's fastest-growing drugs group in sales terms following the launch of its first drug, Tracleer, but it did not achieve profitability until 2003. Similarly, hardly any European biotechnology companies are earning money. Only Serono SA – the Swiss powerhouse of European biotechnology – has a market capitalization to rival US leaders (Firn, 2003). Serono SA grew out of a hormone extraction business with a 50-year record of profitability and is the world leader in the treatment of infertility; it is also well known in endocrinology and the treatment of multiple sclerosis. In 2002, Serono SA made US\$333 million net profit from US\$1,546 million of sales; 23 per cent of the revenue from these sales was devoted to its R&D division, which employs 1,200 people. The Spanish subsidiary of Serono SA in Madrid is now producing recombinant human growth hormone for the whole world, whereas factories in the United States and Switzerland have ceased to produce it. The Spanish subsidiary had to invest €36 million in order to increase its production, as well as another €5 million to upgrade its installations for the production of other recombinant pharmaceuticals to be exported worldwide.

In spite of a wealth of world-class science, the picture in much of Europe is of an industry that lacks the scale to compete and is facing the financial crunch, which may force many companies to seek mergers with stronger rivals (Firn, 2003).

Germany

Germany has overtaken the United Kingdom and France, and is currently home to more biotechnology companies than any country except

the United States. But, far from pushing the boundaries of biomedical science, many companies are putting cutting-edge research on hold and are selling valuable technology just to stay solvent. Until the mid-1990s, legislation on genetic engineering in effect ruled out the building of a German bio-industry. According to Ernst & Young, the more than 400 companies set up in Germany since then needed to raise at least US\$496 million from venture capitalists over 2004 to refinance their hunt for new medicines. Most were far from having profitable products and, with stock markets in effect closed to biotechnology companies following the bursting of the bubble in 2000, they were left to seek fourth or even fifth rounds of private financing (Firn, 2003).

The biggest German biotechnology companies, such as GPC Biotech and Medigene, were able to raise significant sums in initial public offerings at the peak of the Neuer Markt, Germany's market for growth stocks. But when the technology bubble burst in 2000, it became clear to GPC Biotech that investors put very little value on "blue-sky" research. "They wanted to see proven drug candidates in clinical trials", said Mirko Scherer, chief financial officer (cited in Firn, 2003). The only option for companies such as GPC Biotech and Medigene was to buy drugs that could be brought to market more quickly. GPC Biotech has used the cash it earned from setting up a research centre for Altana, the German chemicals and pharmaceutical group, to acquire the rights to satraplatin, a cancer treatment that was in the late stages of development. In October 2003, regulators authorized the initiation of the final round of clinical trials (Firn, 2003). After a series of clinical setbacks, Medigene has mothballed its early-stage research to cut costs and has licensed in late-stage products to make up for two of its own drugs that failed. The strategy will help the company eke out its cash; but cutting back on research will leave little in its pipeline (Firn, 2003).

Many of Germany's biotechnology companies have abandoned ambitious plans to develop their own products and chosen instead to license their drug leads to big pharmaceutical companies in exchange for funding that will allow them to continue their research. This approach is supported by the acute shortage of potential new medicines in development by the world's biggest pharmaceutical companies. But Germany's bio-industry has few experimental drugs to sell – about 15 compared with the more than 150 in the United Kingdom's more established industry. Moreover, most of Germany's experimental drugs are in the early stages of development, when the probability of failure is as high as 90 per cent. That reduces the price that pharmaceutical companies are willing to pay for them (Firn, 2003).

Companies also have to struggle with less flexible corporate rules than their rivals in the United Kingdom and the United States. Listed compa-

nies complain that the Frankfurt stock exchange does not allow injections of private equity, which are common in US biotechnology. As a result, few of Germany's private companies state that they expect to float in Frankfurt. Most are looking to the United States, the United Kingdom or Switzerland, where investors are more comfortable with high-risk stocks. However, many German companies may not survive long enough to make the choice (Firn, 2003).

Faced with this bleak outlook, many in the industry agree that the only solution is a wave of consolidation that will result in fewer, larger companies with more diverse development pipelines. A number of investors in Germany's bio-industry are already pushing in this direction. TVM, the leading German venture capital group, had stakes in 14 German biotechnology companies and was trying to merge most of them. TVM sold off all Cardion's drug leads after failing to find a merger partner for the arthritis and transplant medicine specialists. After raising US\$14.1 million in 2002, Cardion has become a shell company that may one day earn royalties if its discoveries make it to market. UK-based Apax Partners was said to have put almost its entire German portfolio up for sale. The fate of MetaGene Pharmaceuticals, one of Apax's companies, may await many others. In October 2003, the company was bought by the British Astex, which planned to close the German operation after stripping out its best science and its US\$15 million bank balance (Firn, 2003).

GPS Biotech's chief financial officer was critical of the investors who turned their backs on Germany and put 90 per cent of their funds in the United States, when a lot of European companies were very cheap. And although Stephan Weselau, chief financial officer of Xantos, was frustrated that venture capitalists saw little value in his young company's anti-cancer technology, he was adamant about the need for Germany's emerging biotechnology to consolidate if it was to compete against established companies in Boston and San Diego (Firn, 2003).

The United Kingdom

The market for initial public offerings in the United Kingdom was all but closed to biotechnology for the three-year period 2000–2002; it reopened in the United States in 2003. City of London institutions, many of which took huge losses on biotechnology, were reluctant to back new issues and have become more fussy about which quoted companies they are prepared to finance (Firn, 2003).

The United Kingdom is home to one-third of Europe's 1,500 biotechnology companies and more than 40 per cent of its products in development. Although the United Kingdom had 38 marketed biotechnology products and 7 more medicines awaiting approval by the end of 2003,

analysts stated that there were too few genuine blockbusters with the sort of sales potential needed to attract investors' attention away from the United States. A dramatic case is that of PPL (Pharmaceutical Proteins Ltd) Therapeutics – the company set up to produce drugs in the milk of a genetically engineered sheep (Polly). By mid-December 2003, the company had raised a paltry US\$295,000 when auctioneers put a mixed catalogue of redundant farm machinery and laboratory equipment under the hammer. This proved that exciting research (Dolly and Polly sheep) does not always lead to commercial success (Firn, 2003).

The profitable British companies reported pre-tax profits of £145 million in 2003, less than 15 per cent of the US\$1.9 billion pre-tax profits reported by Amgen. By mid-2003, the British biotechnology sector seemed to be coming of age. Investors could choose between three companies that had successfully launched several products and boasted market capitalizations in excess of US\$884 million. Since then they have seen PowderJect Pharmaceuticals plc acquired by Chiron Corp., the US vaccines group, for a deal value of £542 million in May 2003; and General Electric swooped in with a £5.7 billion bid for Amersham, the diagnostics and biotechnology company, in October 2003. Earlier, in July 2000, Oxford Asymmetry had been purchased by the German company Evotec Biosystems for £343 million, and, in September 2002, Rosemont Pharma was acquired by the US firm Bio-Technology General for £64 million (Dyer, 2004).

In May 2004, Union Chimique Belge (UCB) agreed to buy Celltech, the United Kingdom's biggest biotechnology company, for £1.53 billion (€2.26 billion). UCB decided Celltech could be its stepping stone into biotechnology after entering an auction for the marketing rights to Celltech's new treatment for rheumatoid arthritis (CPD 870), touted as a blockbuster drug with forecast annual sales of more than US\$1 billion. After seeing trial data not revealed to the wider market, UCB decided to buy the whole company. The surprise acquisition was accompanied by a licensing deal that gives UCB the rights to CPD 870, which accounted for about half the company's valuation. Göran Ando, the Celltech chief executive who will become deputy chief executive of UCB, stated: "we will immediately have the financial wherewithal, the global commercial reach and the R&D strength to take all our drugs to market." News of the deal, which will be funded with debt, sent Celltech shares 26 per cent higher to £5.42, whereas UCB shares fell 4 per cent to €33.68 (Firn and Minder, 2004).

Celltech had been the grandfather of the British biotechnology sector since it was founded in 1980. With a mixture of seed funding from the Thatcher government and the private sector, the company was set up to commercialize the discovery of monoclonal antibodies that can become

powerful medicines. Listed in 1993, the company made steady progress in its own research operations, but gained products and financial stability only with the acquisitions of Chiroscience in 1999 and Medeva in 2000. It also acquired Oxford GlycoSciences in May 2003 in a deal worth £140 million. The great hopes Celltech has generated were based largely on CPD 870, the arthritis drug it planned to bring to market in 2007 that could be by far the best-selling product to come out of a British biotechnology company. After the UCB–Celltech deal, the group ranked fifth among the top five biopharmaceutical companies, behind Amgen, €6.6 billion in revenue in 2003; Novo Nordisk, €3.6 billion; Schering, €3.5 billion; and Genentech, €2.6 billion (Dyer, 2004; Firm and Minder, 2004). Based on 2003 results, the combined market capitalization of UCB Pharma and Celltech will be €7.14 billion; revenues, €2,121 million; earnings before interest, tax and amortization, €472 million; pharmaceutical R&D budget, €397 million; number of employees, approximately 1,450 (Firm and Minder, 2004).

Celltech is the biggest acquisition by UCB, which branched out from heavy chemicals only in the 1980s. Georges Jacob, its chief executive since 1987, stated that when he joined UCB he found a company “devoted to chemicals, dominated by engineers, pretty old-fashioned and very much part of heavy industry”. UCB had been built entirely on internal growth, and its only other sizeable acquisition was the speciality chemicals business of US-based Solutia in December 2002 for US\$500 million, a move that split the Belgian group’s €3 billion revenues evenly between pharmaceuticals and chemicals. One constant was the continued presence of a powerful family shareholder, owning 40 per cent of UCB’s equity via a complicated holding structure (Firm and Minder, 2004).

UCB made its first foray into pharmaceuticals in the 1950s with the development of a molecule it sold to Pfizer, Inc. This became Atarax, an anti-histamine used to relieve anxiety. The relationship with Pfizer was revived in a more lucrative fashion for UCB following the 1987 launch of Zyrtec, a blockbuster allergy treatment that Pfizer helped to distribute in the United States. Although UCB has a follow-up drug to Zyrtec, it faces the loss of the US patent in 2007. UCB also had to fight patent challenges to its other main drug, Keppra, an epilepsy treatment. With the takeover of Celltech, UCB will gain a pipeline of antibody treatments for cancer and inflammatory diseases to add to its allergy and epilepsy medicines. According to most analysts, the expansion in health-care activities will lead the group to divest itself of its remaining chemical business (Firm and Minder, 2004).

After this takeover and following the earlier acquisition of PowderJect Pharmaceuticals and Amersham by US companies, there is not much left in the United Kingdom’s biotechnology sector except Acambis, another

vaccine-maker, valued at about £325 million, and a string of companies below the £200 million mark where liquidity can be a problem for investors. The industry was therefore afraid it would be swamped by its much larger rivals. Martyn Postle, director of Cambridge Healthcare and Biotech, a consultancy, stated that “we could end up with the UK performing the role of the research division of US multinationals” (cited in Dyer, 2004). According to the head of the Bioindustry Association (BIA), “it is clearly the fact that US companies are able to raise much, much more money than in the United Kingdom, which puts them in a much stronger position” (cited in Dyer, 2004). The BIA called for changes in the rules on “pre-emption rights”, which give existing shareholders priority in secondary equity offerings. Because Celltech was by far the most liquid stock in the sector, there could be a broader impact on the way the financial sector treats biotechnology, including a reduction in the number of specialist investors and analysts covering the sector (Dyer, 2004).

It is important for the United Kingdom to create an environment in which biotechnology can flourish. The industry has called for institutional reform, including measures to make it easier for companies to raise new capital. The British government must also ensure that its higher education system continues to produce world-class scientists. That reinforces the need for reforms to boost the funding of universities. The Celltech takeover need not be seen as a national defeat for the United Kingdom. The combined company may end up being listed in London. Even if it does not, Celltech’s research base in the United Kingdom will expand. Its investors have been rewarded for their faith and, if its CPD 870 drug is approved, UCB’s shareholders will also benefit. But, for Celltech’s executives, the acquisition is a victory for Europe. The takeover creates an innovative European biotechnology company that is big enough, and has sufficient financial resources, to compete globally. “The key was to have viable European businesses that have a sustainable long-term presence,” stated Göran Ando, who confirmed that UCB’s research will be run from Celltech’s old base in Slough (cited in Dyer, 2004). A lot of hopes are riding on the success of UCB and Celltech, which would allow the fledgling bio-industry to thrive in Europe and prevent the life sciences from migrating to the United States (Dyer, 2004).

France

In France in 2003, according to the France Biotech association, there were 270 biotechnology companies focused on the life sciences and less than 25 years old. They employed 4,500 people – a number that could be multiplied four or five times if about €3 billion were to be invested in

public research over three years. In 2003, France invested only €300 million of private funds and €100 million of public funds in biotechnology, far behind Germany and the United Kingdom, which each invested about €900 million per year. In 2003, France launched a five-year Biotech Plan aimed at restoring the visibility and attractiveness of France in 2008–2010. Three areas – human health, agrifood and the environment – were expected to attract the funds as well as the efforts of universities, public and private laboratories, hospitals, enterprises and investors (Kahn, 2003b).

SangStat, a biotechnology company created in 1989 in the Silicon Valley by Philippe Pouletty (a French medical immunologist), is working on organ transplants. It was established in California because, at the time of its creation, venture capital in France was only just starting to support such endeavours in biotechnology. Between FFr 600 million and FFr 2 billion were needed to set up a biotechnology corporation to develop one or perhaps two new drugs, and bankruptcy was very likely in France. SangStat is now a world leader in the treatment of the rejection of organ transplants and intends to extend its expertise and know-how to the whole area of transplantation. It is already marketing two drugs in the United States and three in Europe (Lorelle, 1999a).

A second corporation, DrugAbuse Sciences (DAS), was established by Pouletty in 1994, by which time venture capital was becoming a more common practice in Europe. Two companies were created at the same time: DAS France and DAS US in San Francisco, both belonging to the same group and having the same shareholders. Being established in Europe and the United States, greater flexibility could be achieved from the financial viewpoint and better resilience to stock exchange fluctuations. DAS was able to increase its capital by FFr 140 million (€21.3 million) in 1999 with the help of European investors (Lorelle, 1999a).

DAS specializes in drug abuse and alcoholism. Its original approach was to study neurological disorders in the patient so as to promote abstinence, treat overdoses and prevent dependence through new therapies. Pouletty had surveyed 1,300 existing biotechnology companies in 1994 and found that hundreds were working on cancer and dozens on gene therapy, diabetes, etc., but not one was working on drug and alcohol addiction. Even the big pharmaceutical groups had no significant activity in this area, although drug and alcohol addiction is considered the greatest problem for public health in industrialized countries. For instance, 2.5 per cent of the annual gross domestic product in France is spent on these illnesses, and some US\$250 billion in the United States (Lorelle, 1999a).

A first product, Naltrel, improves on the current treatment of alcoholism by naltrexone. The latter, to be efficient, must be taken as pills every day. But few alcoholics can strictly follow this kind of treatment. In order

to free patients from this daily constraint, a monthly intramuscular injection of a delayed-action micro-encapsulated product has been developed, which helps alcoholics and drug addicts to abstain from their drug. The molecule developed inhibits the receptors in the brain that are stimulated by opium-related substances.

Another successful product, COC-AB, has been developed for the emergency treatment of cocaine overdoses. This molecule recognizes cocaine in the bloodstream and traps it before it reaches the brain; it is then excreted through the kidneys in urine. Commercialization of the medicine was expected to help the 250,000 cocaine addicts who are admitted annually to the medical emergency services. In the long term, DAS intends to develop preventive compounds that can inhibit the penetration of the drug into the brain (Lorelle, 1999a).

DAS was expected to become a world-leading pharmaceutical company by 2005–2007 in the treatment of alcoholism and drug addiction or abuse. This forecast was based on the current figures of 30 million chronic patients in the United States and Europe, comprising 22 million alcoholics, 6 million cocaine addicts and 2 million heroin addicts (Lorelle, 1999a).

Another success story is the French biotechnology company Eurofins, founded in Nantes in 1998 to exploit a patent filed by two researchers from the local faculty of sciences. Eurofins currently employs 2,000 people worldwide and in four years increased its annual turnover 10-fold (to €162 million). Its portfolio contains more than 5,000 methods of analysing biological substances. The company is located in Nantes, where 130 people carry out research on the purity and origin of foodstuffs. Despite the closure of some of Eurofins' 50 laboratories in order to improve the company's financial position in the face of the slowdown in the economy, Eurofins wants to continue to grow.

This success story has led the city of Nantes to think about creating a biotechnology city. It has also given a strong impetus to medical biotechnology at Nantes' hospital, where the number of biotechnology researchers soared from 70 to 675. In October 2003, the Institute of Genetics Nantes Atlantique initiated the analysis of human DNA for forensic purposes. This institute, which received venture capital from two main sources, was expected to employ 50 people within two years in order to meet the demand generated by the extension of the national automated database of genetic fingerprinting (Luneau, 2003).

Spain

Oryzon Genomics is a genomics company based in Madrid. It applies genomics to new cereal crops, grapevines and vegetables, as well as to the production of new drugs (especially for Parkinson's and Alzheimer's

diseases). It is a young enterprise, an offshoot of the University of Barcelona and the Spanish Council for Scientific Research (CSIC), located in Barcelona's Science Park. With a staff of 22 scientists, the company is experiencing rapid growth and is developing an ambitious programme of functional genomics. It was the first genomics enterprise to have access to special funding from the NEOTEC Programme, in addition to financial support from the Ministry of Science and the Generalitat of Catalonia. Moreover, the National Innovation Enterprise (ENISA), which is part of the General Policy Directorate for Medium and Small Sized Enterprises of the Ministry of the Economy, has invested €400,000 in Oryzon Genomics – this was ENISA's first investment in the biotechnology sector. At the end of 2002, Najeti Capital, a venture capital firm specializing in investments in technology, acquired 28 per cent of Oryzon Genomics in order to support the young corporation. In 2003, Oryzon Genomics' turnover was estimated at €500,000, and its clients comprised several agrifood and pharmaceutical companies as well as public research centres.

Japan's biotechnology and bio-industry

Japan is well advanced in plant genetics and has made breakthroughs in rice genomics, but it is lagging behind the United States in human genetics. Its contribution to the sequencing of the human genome (by teams of researchers from the Physics and Chemistry Research Institute of the Science and Technology Agency, as well as from Keio University Medical Department) was about 7 per cent. In order to reduce the gap with the United States, the Japanese government has invested significant funds in the Millennium Project, launched in April 2000. The project covers three areas: the rice genome, the human genome and regenerative medicine. The 2000 budget included ¥347 billion for the life sciences. The genomics budget, amounting to ¥64 billion, was twice that of the neurosciences. Within the framework of the Millennium Project, the Ministry of Health aimed to promote the study of genes linked with such diseases as cancer, dementia, diabetes and hypertension; results for each of these diseases were expected by 2004 (Pons, 2000).

The Ministry of International Trade and Industry (MITI) set up a Centre for Analysis of Information Relating to Biological Resources. This had a very strong DNA-sequencing capacity – equivalent to that of Washington University in the United States (sequencing of over 30 million nucleotide pairs per annum) – and will analyse the genome of micro-organisms used in fermentation and provide this information to the industrial sector. In addition, following the project launched in 1999 by Hitachi Ltd, Takeda Chemical Industries and Jutendo Medical Faculty

aimed at identifying the genetic polymorphisms associated with allergic diseases, a similar project devoted to single-nucleotide polymorphisms (SNPs) was initiated in April 2000 under the aegis of Tokyo University and the Japanese Foundation for Science. The research work is being carried out in a DNA-sequencing centre to which 16 private companies send researchers with a view to contributing to the development of medicines tailored to individuals' genetic make-up. This work is similar to that undertaken by a US–European consortium (Pons, 2000).

On 30 October 2000, the pharmaceutical group Daiichi Pharmaceutical and the giant electronics company Fujitsu announced an alliance in genomics. Daiichi and Celestar Lexico Science (Fujitsu's biotechnology division) were pooling their research efforts over the five-year period 2000–2005 to study the genes involved in cancer, ageing, infectious diseases and hypertension. Daiichi devoted about US\$100 million to this research in 2001–2002, and about 60 scientists were involved in this work of functional genomics (Pons, 2000).

On 31 January 2003, the Japan Bioindustry Association (JBA) announced that, as of December 2002, the number of “bioventures” in Japan totalled 334 firms. This announcement was based on a survey – the first of its kind – conducted by the JBA in 2002 to have a better understanding of the nation's bio-industry. A “bioventure” was defined as a firm that employs, or develops for, biotechnology applications; that complies with the definition of a small or medium-sized business as prescribed by Japanese law; that was created 20 years ago; and that does not deal primarily in sales or imports/exports. The 334 bioventures had a total of 6,757 employees (including 2,871 R&D staff), sales amounting to ¥105 billion and R&D costs estimated at ¥51 billion (Japan Bioindustry Association, 2003). The average figures per bioventure were: 20 employees (including 8.6 R&D staff), sales worth ¥314 million and R&D costs of ¥153 million.

The three regions with the highest concentrations of bioventures were Kanto (191, or 57 per cent of the national total), Kinki/Kansai (55, or 16 per cent) and Hokkaido (32, or 10 per cent). One-third of all ventures (112) were located in Tokyo (within the Kanto region). The most common field of bioventure operations was pharmaceuticals and diagnostic product development (94 bioventures), followed by customized production of DNA, proteins, etc. (78 bioventures), bioinformatics (41 ventures), and reagents and consumables development (38 bioventures).

Australia's biotechnology and bio-industry

In its 2003 global biotechnology census, the consultancy firm Ernst & Young ranked Australia's A\$12 billion biotechnology and bio-industry

as number one in the Asia-Pacific region and sixth worldwide. Australia accounts for 67 per cent of public biotechnology revenues for the Asia-Pacific region.

The Australian government gave a boost to the bio-industry by providing nearly A\$1 billion in public biotechnology expenditure in 2002–2003. There were around 370 companies in Australia in 2002 whose core business was biotechnology – an increase from 190 in 2001. Human therapeutics made up 43 per cent, agricultural biotechnology 16 per cent and diagnostics companies 15 per cent. Over 40 biotechnology companies were listed on the Australian stock exchange (ASX) and a study released by the Australian Graduate School of Management reported that an investment of A\$1,000 in each of the 24 biotech companies listed on the ASX between 1998 and 2002 would have been worth more than A\$61,000 in 2003 – an impressive 150 per cent return. During the same period, shares in listed Australian biotechs significantly outperformed those of US biotechs, and the overall performance of listed Australian biotech companies was higher than that of the Australian stock market as a whole.

Over A\$500 million was raised by listed Australian life science companies in 2003, and the ASX health-care and biotechnology sector had a market capitalization of A\$23.4 billion in 2003, up 18 per cent on 2002. There has been a maturing of the Australian biotechnology sector, with greater attention paid to sustainable business models and the identification of unique opportunities that appeal to investors and partners. The industry is supported by skilled personnel – Australia is considered to have a greater availability of scientists and engineers than the United Kingdom, Singapore or Germany.

Australia is ranked in the top five countries (with a population of 20 million or more) for the number of R&D personnel. In terms of public expenditure on R&D as a percentage of GDP, it outranks major OECD countries, including the United States, Japan, Germany and the United Kingdom (Australian Bureau of Statistics, 2003). For biomedical R&D, Australia is ranked the second most effective country – ahead of the United States, the United Kingdom and Germany – particularly with respect to labour, salaries, utilities and income tax. Australia is ranked third after the Netherlands and Canada for the cost competitiveness of conducting clinical trials.

Australian researchers indeed have a strong record of discovery and development in therapeutics. Recent world firsts include the discovery that *Helicobacter pylori* causes gastric ulcers, and the purification and cloning of three of the major regulators of blood cell transformation – granulocyte colony-stimulating factor (GCSF), granulocyte macrophage colony-stimulating factor (GM-CSF) and leukaemia inhibiting factor (LIF). Australia is cementing its place at the forefront of stem cell re-

search with a transparent regulatory system and the establishment of the visionary National Stem Cell Centre (NSCC). An initiative of the Australian government, this centre draws together expertise and infrastructure; in 2003 it entered into a licensing agreement with the US company LifeCell.

Strong opportunities exist in areas such as immunology, reproductive medicine, neurosciences, infectious diseases and cancer. There are also opportunities for bioprospecting given that Australia is home to almost 10 per cent of global plant diversity, with around 80 per cent of plants and microbes in Australia found nowhere else in the world. Although 25 per cent of modern medicines come from natural products, it is estimated that only 1 per cent of plants in Australia have been screened for natural compounds.

Australia is the most resilient economy in the world, has the lowest risk of political instability in the world and possesses the most multicultural and multilingual workforce in the Asia-Pacific region. Its geographical location has not been a deterrent to the establishment of partnerships. According to Ernst & Young's 2003 "Beyond Borders" global biotechnology report, Australia had 21 cross-border alliances in 2002 – more than France and Switzerland, and 18 more than its nearest Asia-Pacific competitor. All the major pharmaceutical companies have a presence in Australia and pharmaceuticals are the third-highest manufactures export for Australia, generating over US\$1.5 billion. The largest drug-exploration partnership in Australian history, between Merck & Co., Inc. and Melbourne-based Amrad to develop drugs against asthma, other respiratory diseases and cancer, was valued at up to US\$112 million (plus royalties) in 2003. It is therefore no wonder that the pharmaceutical industry in Australia, which has annual revenues of US\$9.2 billion, is increasingly viewed by the main global players as a valuable source of innovative R&D and technology.

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