Frontiers of Biotechnology

By Mitsuru Miyata

The commercialization of biotechnology products has made rapid progress in Japan since the early 1980s. As in Europe and the United States, high value-added pharmaceuticals and diagnostic drugs are in the vanguard of these new products. Biotechnological techniques have made it possible to produce economically even lower-priced products. Japanese companies are contributing greatly to expanding the range of applications for this new technology.

Many Japanese companies, mostly zymogenic enterprises, are pushing research and development on applying biotechnology to fine chemicals, expected to become the next-generation bioindustry. Thanks to techniques they have acquired through the industrialization of amino acid and nucleic acid fermentation, Japanese zymogenic companies lead their competitors in this field.

But Japanese companies lag seriously behind their foreign counterparts in using biotechnology to develop pharmaceutical products. In order to bridge this gap, Japanese companies have concluded nearly 100 contracts to obtain technology from European and American venture firms. This is in sharp contrast to fine chemicals, where Japanese companies conduct R&D with their own technology and where there is a real possibility they will contribute significantly to the development of technology worldwide. Government ministries and agencies, including the Ministry of International Trade and Industry (MITI), are actively encouraging research on applying biotechnology to fine chemicals.

Forging ahead with pharmaceuticals

In December 1985, the Ministry of Health and Welfare placed recombinant human insulin manufactured by genetic engineering on its drug price list for the first time. Subsequently, Shionogi & Co. began marketing recombinant human insulin this year.

This was the first recombinant pharmaceutical product marketed in Japan, although the same product had been put on sale in the U.S. a full three years earlier.

The Ministry is shortly expected to approve human growth hormone and α-interferon (IFN). Clinical trials have been completed, and applications for approval of their manufacture or import have been filed. Initially at least, human insulin and human growth hormone

Table 1
Recombinant Pharmaceuticals under Clinical Trial or for Which Clinical Trial Has Been Completed (As of December 1, 1985)

Pharmaceutical	Developed by	Tie-up partner
Insulin	*Shionogi & Co., Ltd.	Eli Lilly & Co.
Growth hormone (2nd generation)	**Sumitomo Chemical Co., Ltd.	KabiVitrum
	Sumitomo Chemical Co., Ltd.	Eli Lilly & Co.
	Eli Lilly Japan K.K.	Eli Lilly & Co.
α-interferon	**Takeda Chemical Industries, Ltd./ Nippon Roche K.K.	Hoffmann-La Roche, Inc.
	**Yamanouchi Pharmaceutical Co., Ltd./ Essex Nippon K.K.	Schering-Plough Corp.
β-interferon	Kyowa Hakko Kogyo Co., Ltd./ Toray Industries, Inc.	Japanese Foundation for Cancer Research
γ-interferon	Takeda Chemical Industries, Ltd./ Nippon Roche K.K.	Hoffmann-La Roche, Inc.
	Shionogi & Co., Ltd.	Biogen Inc.
	Toray Industries, Inc./ Daiichi Seiyaku Co., Ltd.	Genentech, Inc.
	Kyowa Hakko Kogyo Co., Ltd.	Japanese Foundation for Cancer Research
	Meiji Seika Kaisha, Ltd.	G. D. Searle & Co.
	Suntory Ltd.	Sole developer
Interleukin-2	Takeda Chemical Industries, Ltd.	Sole developer
	Shionogi & Co., Ltd.	Biogen Inc.
Hepatitis B vaccine	Shionogi & Co., Ltd.	Merck & Co., Inc.
	The Green Cross Corp.	Biogen Inc.
	The Chemo-Serotherapeutic Research Institute	Osaka University
Tumor necrosis factor (TNF)	Asahi Chemical Industry Co., Ltd.	Sole developer
	Dainippon Pharmaceutical Co., Ltd.	Sole developer

Notes: * Import was approved by the Ministry of Health and Welfare on October 21, 1985.
** Clinical trial has been completed.

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Table 2 Progress in Development of Monoclonal Antibody Diagnostic Drugs in Japan (As of December 31, 1985)

On sale				
1982	**AFP**	Dainabot Co.	RIA	Approved by MHW
1983	**CEA**	Nippon Roche K.K.	EIA	″
1984	**CEA**	Dainabot Co.	RIA	″
	AFP	Daiichi Pure Chemicals Co., Ltd.	EIA	Research reagent
	T cell, B cell subset	Daiichi Pure Chemicals Co., Ltd.	FIA	Research reagent, applied for approval
	TSH	Boehringer Mannheim	EIA	Approved by MHW
1985	**PAP**	Dainabot Co.	EIA	″
	IgE	Fuji Rebio Co.	EIA	″
	CA-19-9	Toray–Fuji Bionics Co.	RIA	″
		The Green Cross Corp.	RIA	″
	HBs antigen	Immunis Co.	EIA	″
	CEA	Mochida Pharmaceutical Co., Ltd.	EIA	″
		Kainos Laboratories Ltd.	EIA	″
		Ono Pharmaceutical Co., Ltd./ Toyobo Co.	EIA	–
		Wako Pure Chemical Ind., Ltd.	EIA	Research reagent, applied for approval
		Boehringer Mannheim	EIA	Research reagent, applied for approval
	AFP	Mochida Pharmaceutical Co., Ltd.	EIA	Approved by MHW
		Kainos Laboratories Ltd.	EIA	Approved by MHW
	FDP	Daiichi Pure Chemicals Co., Ltd.	EIA	Research reagent, applied for approval
	HBcIgM	Dainabot Co.	RIA	Approved by MHW
	Chlamydia	Daisyva Ltd.	FIA	Research reagent
	hCG	Dia-Iatron Co., Ltd.*	EIA	″
Application for authorization submitted or to be submitted shortly				
	CA-19-9	Toray-Fuji Bionics Co.	EIA	Applied for approval
	CA-125	Toray-Fuji Bionics Co.	RIA	″
		Toray-Fuji Bionics Co.	EIA	″
		The Green Cross Corp.	RIA	″
	γ-seminoprotein	Chugai Pharmaceutical Co., Ltd.	EIA	″
	HBe antigen	Immunis Co.	EIA	Applied for approval
	IgG	Wako Pure Chemical Ind., Ltd.	Nephelometry	″
	TSH	Fuji Rebio Co.	EIA	″
	CA-15-3	Toray-Fuji Bionics Co.	RIA	
	α2-macroglobulin	Mochida Pharmaceutical Co., Ltd.	–	–
	hCG	Mochida Pharmaceutical Co., Ltd.	–	–
	β2-microglobulin	Eiken Chemicals	EIA	–
	Dupan II	Kyowa Medics	EIA	–
	CEA	Sekisui Chemical Co., Ltd.	EIA	–
	Insulin	Sekisui Chemical Co., Ltd.	–	–
	HBs antigen	Dainabot Co.	–	–
	TSH	Dainabot Co.	EIA	–
		Hoechst, Japan	EIA	–

Notes: * Introduced from Hybritech Inc. of the U.S.
MHW stands for the Ministry of Health and Welfare.
RIA stands for radio immunoassay; EIA for enzyme immunoassay; and FIA for fluoroimmunoassay.
Source: *Nikkei Biotechnology*

manufactured by foreign companies will be imported and marketed by Japanese firms. α-IFN will be the first recombinant pharmaceutical product actually manufactured in Japan.

A host of new pharmaceuticals is being developed from substances in the human body through genetic engineering (Table 1). Recombinant pharmaceuticals and new therapies using these drugs are called "biomedics," a term proposed by Dr. Teruhisa Noguchi, director of Biomedical Research Institute of Suntory, and many companies are concentrating on developing biomedical products. Clinical trials have already been conducted on interleukin-2 (IL2), hepatitis B (HB) vaccine, tumor necrosis factor (TNF), β-IFN and γ-IFN. Clinical trials of tissue plasminogen activator (TPA), a thrombolytic agent, erythropoietin, for curing anemia, and superoxide dismutase (SOD), an enzyme that removes activated oxygen, are slated to start soon.

The commercialization of diagnostic drugs developed with cell fusion technology is proceeding even more rapidly than that of recombinant drugs (Table 2). Idioblastic monoclonal antibody, for instance, produced by fusing lymph cells, can identify even slight differences in the stereocomposition of molecules. A great variety of diagnostic drugs capable of high-precision detection and diagnosis of viruses and cancers has been commercialized using this monoclonal antibody.

In Japan, enthusiastic efforts are under way to develop a monoclonal antibody diagnostic drug for detecting cancer through blood tests. Clinical trials started last year on a technique for diagnosing cancer on a display screen with a monoclonal antibody imported by Teijin from Hybritech Co. of the United States. The antibody is combined with a radioisotope and injected into the body, with the radioisotope showing up on the display screen as the antibody carries it to the tumor.

Research has also begun on using monoclonal antibodies to treat cancer and infectious diseases. Teijin, Morinaga & Co., Chugai Pharmaceuticals, Suntory, Takeda Chemical Industries and Green Cross Corp. are racing to achieve breakthroughs in this field.

Leading in fine chemicals applications

Some of the most promising experiments in applied biotechnology involve fine chemicals like amino and nucleic acids. Amino acid makers Ajinomoto, Kyowa Hakko Kogyo and Tanabe Seiyaku have taken the lead in applying gene manipulation and cell fusion to improve microbes used in industrial production. With their long experience in fermentation technology, these and other companies have succeeded in raising the productivity of such amino acids as threonine, phenylalanine and tryptophan by genetically engineering amino acid-producing bacteria like *Brevibacterium*. Takeda and others have also succeeded in applying genetic engineering to the fermentation of nucleic acid.

In the absence of industrial guidelines on genetic engineering, many Japanese companies are postponing industrialization of the products they have created. In 1986, however, MITI is expected to compile guidelines on the industrial applications, paving the way for accelerated commercialization of genetic engineering products in the fine chemicals field.

When the bacteria used for genetic engineering and the genes to be combined belong to the same family of microbes, the recombination is termed self-cloning. The present guidelines do not apply to self-cloning, as it is considered a natural phenomenon. Since 1983, Mitsui Toatsu Chemicals has been using self-cloning to produce L-tryptophan, the world's first amino acid produced by genetic engineering.

Cell fusion technology has enabled Meiji Seika to make bacteria capable of mass producing a herbicide. The company put the product on the market in 1984, and is now engaged in joint research with Biogen Co. of Switzerland to further improve production efficiency.

Japan is also well along the path to commercializing bioreactors, bacteria and enzymes immobilized without resorting to genetic engineering or cell fusion technology. In 1969, Tanabe Seiyaku became the first company in the world to industrialize a bioreactor.

In order to promote the application of biotechnology to fine chemicals, MITI has commissioned research to 14 companies under its next-generation basic technology research and development program. Research is under way on genetic engineering, bioreactors and cell mass-culture technology under a ten-year program launched in 1981. Mitsubishi Chemical Industries has already succeeded in using a bioreactor to produce muconate, the raw material of functional polymer.

Sumitomo Chemical successfully used genetic engineering to introduce the cytochrome P450 gene, whose product is the oxidation enzyme, into yeast. Sumitomo plans to use this recombined yeast to develop a process for adding oxygen to a variety of aromatic compounds. In one test, the company succeeded in transforming acetanilide into acetaminophene, an antipyretic.

Efforts are being made in Japan to develop a monoclonal antibody diagnostic drug that will allow cancer detection through blood tests.

Since 1983, MITI has made grants from its industry revitalization technology assistance fund to an association organized by seven private companies for improving manufacturing processes for fine chemicals with biotechnology. Meanwhile, the Basic Technology Research Promotion Center, a special corporation established by MITI and the Ministry of Posts and Telecommunications, will also invest in a Protein Engineering Research Institute to be established by Toray and other private companies this year. The institute will promote research on protein engineering to develop innovative chemical industrial processes.

Applications in the food industry

Japan lags behind in applications of genetic engineering to foodstuffs. However, research on culturing yeast strains to brew *sake* (rice wine) and *shochu* (distilled spirits), and on cold-resistant bread yeast, is much further along. Leading *sake* breweries and yeast makers are taking the initiative in yeast research. Meiji Milk Products and Yakult Honsha Co. are both researching genetic engineering of *Lactobacillus*, which triggers lactic fermentation in yogurt and other lactic drinks. But many companies are wary of applying genetic engineering to foods because of bitter past experience. The industry has already seen the commercialization of single-cell proteins blocked by consumer movement opposition.

Progress is being made, however, with plant tissue culture and bioreactors. Nitto Electric Industrial Co. plans to test-market ginseng mass produced with tissue culture technology this year. In fact, Japan leads the world in the tissue culturing of plants. Mitsui Petrochemical Industries is already making pigments and medical raw materials produced with tissue culture technology on a commercial basis. The National Food Research Institute of the Ministry of Agriculture, Forestry and Fisheries perfected the world's first technology for industrializing high fructose syrup by using bioreactors of immobilized enzymes. Meiji Seika and Mitsui Sugar Co. soon followed suit with the new sweeteners fructooligosaccharides and palatinose. These new sweeteners have lower caloric content and cause less tooth decay than natural sugars.

Other recent research includes bioreactors to shorten fermentation time for soy sauce, beer and wine. Japanese achievements in this field are attracting wide attention. The Ministry of Agriculture, Forestry and Fisheries, like MITI, is commissioning research to private companies under its program for technological innovation in the food industry.

Lagging behind in agriculture

Japan has fallen behind other countries in agricultural applications of biotechnology, even though it is felt that this is the field in which the new technology will have the greatest impact. The lag is in part attributable to Japan's relatively low self-sufficiency in agricultural products, except for rice, and to the limited domestic demand for agricultural biotechnology. The Japanese government's virtual monopoly on research into new rice strains has also played a part.

However, in late 1984 the Ministry of Agriculture, Forestry and Fisheries began joint research on culturing rice strains with Mitsubishi Chemicals and other private companies.

Conversely, research on biotechnology is well advanced in fisheries, a reflection of Japan's status as a leading fishing nation. Kyowa Hakko has developed salmon and eel growth hormones by means of genetic engineering. It will start outdoor tests on stimulating fish breeding later this year.

BIDEC (Bio Industry Development Center), an association of companies engaged in bio-related businesses, estimates that Japan's bioindustrial market will be worth ¥15 trillion ($83.3 billion at the rate of $1/¥180) by the year 2000. This ¥15 trillion will break down into ¥3 trillion for pharmaceuticals, ¥2.5 trillion for chemicals, ¥4 trillion for foods, ¥2 trillion for agricultural, forestry and fishery products and ¥3.5 trillion for other fields.

As the U.S. Congressional Office of Technology Assessment has pointed out, Japan may well have the greatest potential for biotechnology research and development of any country next to the U.S., even though its capabilities differ from industry to industry. Notwithstanding, the Japanese government's investment in bio-related basic research is far smaller than that of the U.S., a fact which may adversely affect the development of biotechnology in Japan. Without appropriate support, Japan cannot be too optimistic about her future international competitiveness in biotechnology. ●