The Japanese Challenge in Biotechnology

Japan is forging ahead, but not as fast as many in the United States think

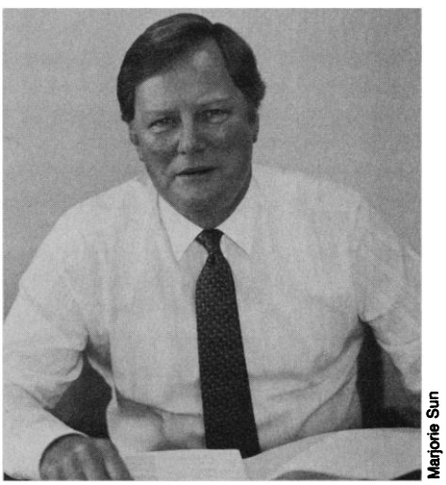
At a scientific meeting in 1981 in San Francisco, Genentech researchers presented a slide that showed for the first time the chemical blueprint for gamma-interferon, a potential therapy against cancer and other diseases. "That's when the cameras came out," says David Goeddel, one of Genentech's senior scientists. Among the picture takers at the public meeting was a scientist from Suntory, a major Japanese food company. To the surprise of Goeddel and others, Suntory then used the information to synthesize gamma-interferon within 6 weeks, displaying unexpected technical capability. "Now no one presents sequencing slides at meetings, or, if they do, they flash them very quickly," says Julian Davies, a scientist and former executive at Biogen. Suntory, like other Japanese companies, "has been very aggressive" in biotechnology, Davies says.

Japan has made great strides in genetic engineering and with remarkable speed even without a strong program in basic biotechnology research, according to many industrial and academic leaders in biotechnology. During the past few years, Japanese scientists were the first to clone and express interleukin-II, which may have therapeutic importance; Ajinomoto, the world's principal producer of monosodium glutamate, licensed interleukin-II to Hoffmann-La Roche last year; and Asahi Chemical Company synthesized tumor necrosis factor, a potential anticancer agent, about the same time as American companies.

These and other achievements have created substantial unease among American scientists and government officials about the challenge posed by Japan in the commercialization of biotechnology. But many experts argue that this apprehension is somewhat overblown. Interviews with industry officials and biotechnology analysts suggest that while Japan has clearly narrowed the gap, it still has a considerable way to go to catch up.

Japan's gains are often attributed to several factors: Japanese companies have struck numerous agreements with American biotechnology companies and through them learned a lot; the Japanese government, industry, and academia are working cohesively to exploit genetic engineering; the country's history of fermentation of food products gives it a distinct commercial advantage; and Japan recruits heavily from overseas and sends many of its own to the United States for training.

But it is not clear, for example, how much U.S. technology has been transferred to Japan through contracts. During the past several years, U.S. biotechnology firms and institutions have signed dozens of contracts with Japanese companies. When the American firms were first getting their feet on the ground in the late 1970's and early 1980's, some of them, such as Genex Corporation, agreed to conduct research and development for Japanese companies in exchange for badly needed capital. In some of these arrangements, Japanese companies sent researchers to train side by side with American experts. Genex chairman Leslie Glick says, "If it wasn't for Japan, a lot of entrepreneurs in the U.S. wouldn't have made it" because the more established American companies were not investing in the same way.



Marjorie Sun

Robert Fildes of Cetus

Looking to market products, but minimize technology transfer.

But most of the contracts are for licensing rather than R&D, according to Mark Dibner of Du Pont, who reported in a 20 September *Science* article, and Susan Clymer, who has examined the Japanese challenge for the Berkeley Roundtable on the International Economy. Their data also show that in a majority of the agreements, American firms or institutions have licensed products and marketing rights, not technology to the Japanese.

Richard Flavell, research director at Biogen in Cambridge, Massachusetts, which has several agreements with Japanese companies, says that in the past, the licensee "has been given the recipe for manufacturing because in the early stages, Biogen couldn't meet the demands for manufacturing. Some trade secrets, a lot of little tricks that we use" are exchanged, he concedes. "It's a trade-off between money and preventing the transfer. But when information is disclosed, the Japanese "could read half of it in the open literature anyway," he says. Now, however, "we're moving away from licensing technology and more towards products" because in the long run Biogen develops its own manufacturing capability and benefits more financially, Flavell says.

Other companies have struck agreements sparingly or not at all to prevent technology transfer to competitors in general, not only Japan. Genentech, based in South San Franciso, has several contracts with Japanese companies, but has only licensed products, not technology, according to Clifford Orent, Genentech's vice president for international marketing. Cetus, located across the bay in Emeryville, had not licensed any products or technology to Japan until August. "We never needed the money," says Cetus chairman Robert Fildes. Now, like other companies, it has products coming online and needs a commercial partner in Japan to coordinate clinical testing and marketing. Fildes says that product licensing involves a "minimum of technology transfer." Even if another company is given the manufacturing instructions, "that's only a defined set of techniques. You're not going to teach them basic research, such as how you constructed a certain organism," which is the key information. Zachary Wochok, president of Plant Genetics, a young firm located in Davis, California, notes that when his company struck a recent deal with Kirin Breweries, "they brought some technology to the table too."

Now the number of agreements struck seems to be dwindling, according to Clymer, and a 1984 article in the *Japan Economic Journal*, the Japanese equivalent of the *Wall St. Journal*. Clymer is manager of business development at Bioresponse, a firm in Hayward, California, and wrote the section on Japan in the exhaustive 1984 report by the Office of Technology Assessment on biotechnology. The *Journal* article quotes a

spokesman for Kyowa Hakko Kogyo, a chemical company, saying, "There aren't any more techniques for which joint research can be made." This suggests in part that the Japanese are more inclined to strike out on their own in research and that they have improved their own technical capability to clone and express genes. But, in the view of Davies of Biogen, the drop in licensing also indicates that the interest in the kinds of agreements has shifted. Like American and European companies, they want to license products, not technology. Japanese companies "are not so willing to take a flyer anymore and buy ideas like they did early on," he says. "They're not so willing to gamble."

At the very least, Japanese companies bought time by licensing, says Walter Gilbert, cofounder of Biogen. The Japanese decided early on that "this new technology was going to work," he said, while established American companies "sat back to watch what would happen" with biotechnology. Japanese companies also decided they could not create the first generation of products, so they licensed and turned their efforts towards the second generation, he said.

The Japanese government is widely viewed as the driving force behind the country's jump forward in biotechnology. In 1981, Japan's Ministry of International Trade and Industry (MITI) laid out a brand new 10-year program targeting several specific areas for collaboration, including the development of DNA synthesis techniques, improved vessels to grow microbes in large volume, and better mass cell culture techniques. Several other agencies and ministries subsequently set up their own programs. These programs mainly fund research at universities and government research laboratories and encourage collaboration between these two sectors and companies and among companies themselves.

The government made a big splash with the announcement of the programs. But its efforts should be kept in perspective, according to observers. The Japanese government spends far less on biotechnology basic research than the United States. MITI budgeted $130 million for its program, but that is for a 10-year period. Dibner in his *Science* article points out that the Japanese government in 1984 spent only $50 million to $60 million for biotechnology research related to pharmaceuticals, about one-tenth of that spent by the United States. More than half of this funding in Japan went for applied research. The biggest comparable U.S. program in applied research is a $20-million, 5-year plan funded by the National Science Foundation, according to Dibner. The program is run by the Massachusetts Institute of Technology.

Clymer has said that the Japanese government's funding "should not be overstated." She says that its most important contribution has been to encourage the industry's long-term commitment and set up collaborative projects that bring together companies from different sectors, such as the chemical and drug industries, to work on common problems. Through these projects, she says, a broader segment of Japanese industry—chemical, drug, and food companies—are learning to apply genetic engineering techniques to their individual needs.

But even the impact of this government assistance is questioned by a 1984 report on biotechnology in Japan by an analyst at the Japan Economic Institute, a think tank funded by the Japanese Foreign Ministry. Jon Choy, a staff analyst at the Washington, D.C.–based institute, reported, "In comparison with the United States or Europe, the Japanese government plays a smaller role."

His report indicates that the collaborative projects have had limited success. To participate in these programs and get government contracts, private companies must hand over relevant proprietary information. "While this is excellent for companies new to a field or behind in research, firms with leading-edge technology have not become involved [in certain projects]. . . . "

Furthermore, the cooperative research contracts "are not very favorable" to participants because they only cover direct costs, not overhead or capital equipment. Any patents resulting from the project are owned by the government, "a major disincentive to private participation," Choy said. Yasuo Iriye, an official at Otsuka, Japan's third largest pharmaceutical company, says that companies collaborate "if the project is a long shot, if you can only accumulate a capability" through a joint venture. "But if it's a very good project, a company will likely conduct its own research," he says.

The government's success at encouraging team play between academics conducting basic research and companies appears to be limited, too. Even though most research in biotechnology in Japan is conducted by companies, an advisory panel to MITI on biotechnology reported last year that it is "crucial" to the growth of Japan's biotechnology industry to promote joint basic research and the exchange of information between universities, research institutes, and companies. But Iriye says that industry consulting by university researchers is still widely frowned upon in Japan.

The Japanese government has even been considered a significant hindrance to the advance of biotechnology, Choy and others say. Until recently, it imposed stringent controls on recombinant DNA research. A decade ago, after the National Institutes of Health set rigorous standards to control recombinant DNA research in the United States, Japan, in turn, issued its own that were even tougher. As NIH has relaxed its guidelines, Japan slowly has followed suit. As of last year, Choy reports, government permission was still required to splice genes in plants and animals, although American and European governments have allowed this kind of work for several years.

Many industry leaders also question whether Japan's history in fermentation of soy sauce, amino acids, and antibiotics will help substantially in the scale-up of biotechnology products, at least in the pharmaceutical area. If it is any indication, none of the major American biotechnology firms interviewed has tried to license Japanese fermentation technology. "There's a tremendous myth about Japanese excellence in fermentation technology" and the advantage that affords them, says Charles Cooney, an engineering professor at MIT and a con-

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Japanese Know-How

Japan is ahead in some areas of biotech, but not in others that are just as important, says a recent Commerce report.

sultant to Genentech in fermentation technology. "They've done a superb job in the fermentation and recovery" of amino acids and antibiotics, "but that doesn't necessarily give them an advantage in the production of large proteins" of potential therapeutic importance.

These large proteins, such as tumor plasminogen activator, may have to be produced by mammalian cell culture to get the right configuration and chemical content. Mammalian cell culture, however, is a new and different technological challenge from microbial cell culture, the foundation of Japan's fermentation processing, because animal cells are much more difficult to grow. In addition, says the head of Cetus's research and development, Behzad Khosrovi, the techniques for extraction and purification of the proteins from mammalian cell culture are "crucial," and the methods vary from one product to the next.

One area where Japan's know-how in microbial fermentation might make a difference is in areas other than pharmaceutical production. Khosrovi notes that in the manufacture of commodity chemicals, such as amino acids, where the profit margin is low, new methods of production through genetic engineering and fermentation might cut costs. In this area, the Japanese could be "formidable," Khosrovi said.

A recent study for the Commerce Department provides an in-depth evaluation of Japanese capabilities in other key fields of biotechnology. It was conducted by several American scientists, including Cooney of MIT, Gordon Sato of the Alton Jones Cell Science Center, and David Jackson of Genex, who analyzed their own areas of specialty. Their study was based on a review of English and Japanese publications and scientific literature. The sense of the report is that the Japanese are charging ahead in some fields of biotechnology but not in others that are just as significant.

According to the report, the Japanese are just as knowledgeable as Americans in many areas of recombinant DNA technology, but Japan still lacks sufficient funding and scientists to leap ahead of the United States in basic research. In protein engineering, the Japanese are far behind the United States. Protein engineering is a new field of research aimed at modifying the structure of a protein to produce new or improved substances, such as hormones or interferon. In biosensor research, they are making gains and may be "stiff competition" for the United States in the future. Scientists hope to modify enzymes for diagnostic purposes in medicine, for example.

In those areas where the Japanese have made gains, they have done so partly because universities and companies have been training more scientists in basic biomedical research at home and abroad. The number of biotechnology researchers at Japanese companies has increased annually by 10 percent, according to the MITI advisory panel.

Japan already has some excellent and eminent basic researchers in biotechnology, Americans observe. Several Japanese scientists have conducted key research in cloning and replication. Training overseas, however, is the main way that Japanese researchers from universities and companies are getting up to speed in basic research. Rosters of foreign scientists at the National Institutes of Health show that Japan has sent the most researchers of any one country for the past few years.

> There's a tremendous myth about Japanese capability in fermentation, says Cooney of MIT.

This year, for example, more than 200 visiting Japanese scientists are working at NIH in various biomedical fields. Companies send staff scientists here to train and often to American labs headed by key researchers of Japanese descent, including Keiichi Itakura at the California research institute City of Hope and Masayori Inouye at the State University of New York at Stony Brook. Asahi Chemical Company, for example, sent researchers to train at City of Hope as part of a collaborative project. As a result, the scientists cloned and expressed tumor necrosis factor shortly after they returned to Japan.

There is an impression that Japanese companies recruit heavily from overseas, but this occurs infrequently, according to academic and industry leaders. There are two notable examples of recruitment. Suntory successfully wooed a top young Japanese scientist, Shogii Tanaka, from Itakura's lab to head its new biotechnology program a few years ago.

Otsuka is one company that has recruited vigorously. Last year, it opened up a new biotechnology laboratory in Shady Grove, Maryland, a suburb of Washington that is a couple of miles from NIH and biotechnology companies. Since it has been in business, Iriye, its director, has hired 20 scientists from NIH, Genex, and other laboratories.

Based on Japan's successes in manufacturing of cars and electronics, there is a feeling in the American biotechnology community that Japan could well surpass the United States in the use of genetic engineering, too. But several factors work against the Japanese. Choy says that Japan lacks experience in the international pharmaceutical market. The Japanese drug industry is heavily regulated by the government. Japan does not have the broad base in fundamental research, which is still considered crucial by Japanese and Americans to the commercialization of biotechnology. Cooney of MIT also points out that there is a lack of venture capital in Japan. According to MITI's advisory council on biotechnology, Japanese companies have increased funding for biotechnology development by 20 percent, but the absolute amount is still small. Although major Japanese companies have started up significant biotechnology programs, so have American corporations, such as Monsanto, Eli Lilly, and Du Pont.

"The comparison made between the Japanese computer industry's growth and the future of the bioindustry does not hold," Choy contends. "Spending levels are much lower in bioindustry and it does not lend itself to rapid quantum leaps." The MITI advisory council noted some of the same weaknesses and, in addition, pointed out that Japan does not have a very good system to collect and build gene resources such as the American Type Culture Collection. Given these kinds of difficulties, Japan's "prospects are not necessarily optimistic," the council said.

Nonetheless, the Japanese are still viewed as forging ahead with tremendous speed and success in genetic engineering. Robert Swanson of Genentech has described the U.S. lead as "fragile." While Japan has made some significant gains and is up to speed in some fields of biotechnology, it still is behind the United States as a whole. Yet it would be wrong to discount their challenge entirely. Flavell of Biogen and Khosrovi of Cetus say Japan will get ahead by making processing more efficient. Companies there will make small, discreet improvements, but a large number of them. When innovation in biotechnology ceases "to be the limiting step," as is now the case, Flavell says, "then Japan becomes the greatest threat." As the experts' report to the Commerce Department concludes, there is a "clear need" to keep close tabs on Japan's commercialization of biotechnology.

—MARJORIE SUN