

Like many other Japanese companies, Toyo Jozo, an integrated alcoholic drinks manufacturer, began producing antibiotics in the late 1940s. It continues its expansion into production of selected pharmaceutical and diagnostic enzyme products through proprietary fermentation technology. Today more than half of the company's total sales come from pharmaceutical products. Like other contenders in pharmaceuticals, Toyo Jozo was hurt by the price cuts imposed upon the drug industry in Japan. It intends to build upon its strength in the use of immobilized enzymes, and develop immunosuppressant and anti-cancer products through biotechnology.

Japanese dairy companies are moving aggressively into medical biotechnology, with assistance from the government. MITI's Fermentation Research Institute has pro-

duced an anti-hypertensive drug from casein, a protein extracted from milk. Although the product is less effective than some of its competitors, it is considered safer to use because of its natural origin.

Snow Brand is one of a handful of dairy-related companies with hopes of penetrating pharmaceutical markets through biotechnology. The company, which manufactured penicillin two decades ago, decided to move back into pharmaceuticals early in 1981. It formed a drug planning unit partly in reaction to falling or stagnant sales in such mainstream business areas as seasonings, milk, and dairy foods. Snow Brand's new biotechnology laboratory, completed last year at Ishibashi, includes 60 scientists and 40 technicians at work on dietary products designed for those with inherited errors of metabolism. These

## INTERFERON IN JAPAN: FIERCE COMPETITION

Detractors would say that some Japanese companies are just dabbling in interferon for the sake of public relations. But many are working in earnest, like Kyowa Hakko, whose target is large-scale commercial production of beta and gamma interferons by expression in *E. coli* within the next three to four years. One of the most advanced companies in the field, Kyowa Hakko is benefiting from an impressive history in fermentation and purification—and production facilities spread over 300 acres in Yamaguchi Prefecture will do much to launch it into the market.

Kyowa researchers have completed Phase I toxicity trials using beta interferon made in *E. coli*, and recently started a Phase II clinical trial against various forms of cancers. One of the centers involved in this trial is a Tokyo hospital run by the Cancer Institute of the Japan Foundation for Cancer Research, which licensed its expertise in interferon cloning and expression to Kyowa in 1981.

Tadatsugu Taniguchi, head of the Institute's Biochemistry Department, is one of Japan's youngest top biotechnology researchers; he was first in the world to clone the human beta interferon cDNA, in 1979. Taniguchi's group has recently cloned the gamma interferon gene, and suggested that it may be polymorphic. Taniguchi is not confident about predicting the most likely therapeutic role for interferon. But he admits, "In Japan, most attention is being directed to cancer rather than viral diseases because of the obvious reason—the commercial market is much bigger."

Another company working jointly with the Cancer Institute's genetic engineers is one of Japan's major synthetic fibermakers, Toray Industries. Hoping to benefit from a ready-made drug market, it joined the Daiichi Pharmaceutical Company in 1978; the Toray-Daiichi combination will be the first in Japan to market interferon. Their application for new drug sales is currently under review by the government. Toray's interferon production plant in Mishima City, Shizuoka Prefecture, is expected to begin manufacturing soon.

The company will market natural beta interferon produced in tissue culture from human fibroblasts, a production technology far less advanced than that of cloning and *E. coli* expression. Natural interferon producers also must

live with the fact that their product lacks purity. But the Toray team, under Shigeyasu Kobayashi, whose interferon work dates back more than 20 years, claims 60 percent purity. While this compares unfavorably with the 99.5 percent purity of the company's *E. coli*-made protein, it is nevertheless the world's highest.

The work at Toray is especially notable for its prudence. The company commissioned wide-ranging clinical trials using natural beta interferon that have been running since late 1978. Its application for approval is based on the surprisingly good results obtained in these trials. The researchers achieved a 90 percent disappearance rate with repeated direct injection against viral warts of the skin. A double-blind trial with local administration against herpes viruses also proved effective, they claim. A Phase II trial against such brain cancers as glioblast and medulloblast, diseases that cannot be treated conventionally, attracted considerable interest when it obtained 20–35 percent efficacy. Sixty percent efficacy was also reported against melanoma tumors of 1 cm or less. Trials at Tokyo University's Medical School also showed good results with hepatitis B, a common disease in Japan.

The Hayashibara Company, using a striking, simple production technique, is preparing extensively for commercial production. Forgoing gene recombination technology, the Hayashibara scientists, in association with others at Kyoto Prefectural University's Medical School, are using hamsters to mass-produce human tumor cells that make gamma interferon. Financing for the project, which includes a new \$10 million manufacturing plant, comes from the company's profits in real-estate, maltose production, and technology licensing. Says a company spokesman, "We are still quite a few years away from making profits from interferon. Our policy is to invest 10 years ahead of when we expect the investment to pay off."

Pouring their whisky profits into biotechnology, Suntory is aiming at heading the field of interferon producers. Spiriting away some of the world's top scientific talent, the company has synthesized beta interferon chemically in preparation for large-scale commercial production. Some other top establishments striving for a place in the interferon niche include Yamanouchi Pharmaceuticals, Takeda Pharmaceuticals, Green Cross, Asahi Chemicals, Meiji Seika, Mochida Pharmaceuticals, Shionogi (in collaboration with Biogen), Nippon Roche, and Sumitomo Chemicals.

Competition is fierce. As one expert claims, "Japanese companies have been equally or even more zealous than their overseas counterparts with excessive investment in interferon research and development." A backlash may well follow. The Japanese don't like poor economic performers.

—Alison M. Murray