Genentech wins in Japan

Tokyo

IN a dramatic display of enforcement of Japan's first court ruling on recombinant DNA technology, bailiffs of Osaka District Court last week marched into the Katata plant of Toyobo Ltd to shut down production and seize supplies of a lucrative heart-treatment drug called tissue plasminogen activator (TPA) that is produced using genetic engineering techniques. The court, in a landmark decision, has ruled that Toyobo's sale and production of the drug infringes the patent rights of the US company Genentech Inc.

Genentech and some US observers have hailed the court decision as a sign that Japan is now serious about protecting intellectual property rights. But Japanese experts on the biotechnology industry say the decision, which runs counter to court rulings against Genentech in the United Kingdom and Germany, is flawed and based on an inappropriate decision by the Tokyo patent office.

Although TPA has not turned out to be the blockbuster drug of the biotechnology industry that some predicted, sales of the high-priced drug in Japan have been running at about ¥750 million (\$5.8 million) a month since the drug was put on the market in May. Individual doses (40 mg) of the drug, which helps to dissolve blood clots, are priced at ¥315,000 (\$2,250) each, comparable to the price in the United States.

The market is shared by several companies. Mitsubishi Kasei Corporation, in partnership with Tanabe Seiyaku, and Kyowa Hakko have licensed TPA technology from Genentech, while Daichi Pharmaceutical, in partnership with Toyobo, has been using technology from Genzyme Corporation of the United States.

Long before these companies started production, Genentech filed suit in the Osaka district court in 1987 alleging patent infringement by Toyobo (see *Nature* 333, 587; 1988). And the court has now ruled that the Genzyme technology used by Toyobo does infringe Genentech's Japanese TPA patent, which was awarded by the Tokyo patent office in January.

"We are pleased with the Osaka court's forceful action in protecting our intellectual property rights," says G. Kirk Raab, president and chief executive officer of Genentech. "If this type of fair treatment is displayed in similar cases throughout the appeals process, then Japan will indeed be signalling the worldwide biotechnology industry that meaningful protection, backed by strong remedies, is honoured in

Japan".

But Mitsuru Miyata, editor of the influential newsletter *Nikkei Biotechnology*, says that the TPA court decision is not a good example of recent attempts by Japan to improve its patent system. He points out that Genentech's original TPA patent application had an error in the N-terminal region of the amino acid sequence but the Tokyo patent office allowed the US company to modify its application and remove the part in error while retaining the key part of the amino acid sequence that covers the active part of the TPA molecule. He says the error in the N-terminal region indicates that Genentech's original patent application "seems to be immature" and the Tokyo patent office's subsequent decision to grant the patent followed "bad logic". He also notes that courts in the United Kingdom and Germany rejected TPA patent claims by the US company that were based on the incorrect sequence.

A Toyobo spokesman says there will be an appeal against the court decision. The company is also fighting the Tokyo patent office's award of a TPA patent to Genentech. But a reversal of the decisions is unlikely, observers say, and last week's decision is expected to help Genentech in another court case in Japan against Sumitomo Pharmaceutical Co. Ltd, which has licensed TPA technology from the Wellcome Foundation of the United Kingdom. Sumitomo has yet to win marketing approval from the Ministry of Health and Welfare for its version of the drug.

With the closedown in TPA production, Toyobo and its partner Daichi Pharmaceutical will lose about ¥250 million (nearly \$2 million) a month in sales of TPA; Toyobo has invested more than ¥10,000 million in TPA production facilities and the licence agreement with Genzyme.

David Swinbanks

Solving a dispute, Japanese style

Tokyo

WHILE Genentech of the United States adopted the typical US approach of fighting in the courts to settle its patent dispute over TPA with Toyobo (see above), a group of Japanese companies have solved a patent dispute with Toyobo over another lucrative recombinant DNA drug, erythropoietin (EPO), in typical non-confrontational Japanese style.

Two weeks ago, after inter-company negotiations outside the public eye, Toyobo asked the Ministry of Health and Welfare to withdraw the company's product license approval for EPO. In doing so, Toyobo has shut itself out of a market for EPO in Japan, which is currently worth ¥42,000 million (\$325 million) a year and is rapidly rising. This request to have its license revoked might seem odd to Westerners, but to Japa-

nese it is the only honourable way out of a dispute that Toyobo cannot win.

As in the case of TPA, Toyobo had licensed EPO technology from Genzyme Corporation of the United States. Meanwhile, three other Japanese companies — Kirin beer company, Snow Brand Milk and Chugai Pharmaceutical — have licensing agreements with other US biotech companies and are selling EPO in Japan. Chugai, which has a licensing agreement with Genetics Institute, is in a particularly strong patent position, while Toyobo's position is weakest, observers say. Hence Toyobo's decision to withdraw.

The EPO case also draws attention to the enormous market for this drug in Japan. EPO is a kidney cell glycoprotein that stimulates red blood cell production. It is used to treat patients with chronic renal (kidney) failure.

Because brain death is not recognized in Japan and, as a result, organ transplants are rare, there is a rapidly growing population of patients with chronic renal failure in Japan who are unable to get kidney transplants and who have to get regular (and expensive) dialysis treatment with EPO to survive. The current population of patients is about 100,000 and the number is rising by about 10,000 annually.

The market for EPO in Japan is expected to rise to about ¥70,000 million (\$540 million) per year in the next few years before levelling out because of an expected fall in price of the drug. This situation contrasts with countries such as the United Kingdom where kidney transplants are freely available and the EPO market is negligibly small in comparison.

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