Making Interferon: Gains Come Slowly

Inside the newly built annex of Flow Laboratories in suburban Washington, six scientists stand silently in a semicircle, gazing in awe at 20 liters of ruby red solution swirling in a glass vat. The whirlpool of liquid contains millions of microscopic beads coated with a single layer of slender cells. The cells are human fibroblasts that produce interferon.

Interferon is considered hot property by Wall Street analysts, and stocks rise and fall on news of progress in manufacturing the precious protein. But its value in cancer therapy is still unknown because so little has so far been produced. One of the companies that recently received major manufacturing contracts from the National Cancer Institute is Flow General Laboratories. Its parent company recently reported a rise in net income and a stock split.

Flow's first task has been to understand the idiosyncrasies of fibroblasts as it scales up from laboratory to commercial production of interferon. "Tissue culture is alchemy," says Victor G. Edy, 32, the British scientist whom Flow wooed from the University of Berne, Switzerland, to direct its interferon lab. "Scaling up has been very difficult and frustrating."

A technician found, for example, that the fibroblasts seem to grow best in a medium with less serum supplement than usually required by monolayer cell cultures. A special stirring mechanism was needed to keep the beads in the glass vat buoyant and the culture environment uniform. In the end, Flow scientists designed their own device by modifying a conventional outboard motor propeller.

The fibroblasts are derived from the foreskins of newborns. Although all fibroblasts apparently produce interferon, foreskins are an inexpensive source of cells and readily available, says Don Augustein, a Flow scientist. Flow's fibroblasts were generated specifically from the foreskin of an anonymous newborn whose cells were developed into a cell line by Jan Vilchek at New York University School of Medicine.

Edy admits to several problems in production, but "none of them in itself is insuperable," he says. But in combination they have "given me gray hairs," the young scientist says. Edy is concentrating, in part, on improving cell growth on the beads. Seen under a microscope, the long fibroblasts appear to encase many of the tiny spheres, but some of the beads are bare, which means wasted effort and expense to Flow.

Edy is also worried about the final step of production—lyophilizing or freeze-drying the interferon. Small samples have been successfully processed, but large batches have not been tried. "If I lost 5 billion units, I'll die," he says.

It was a breakthrough 4 years ago in bead technology that set Flow on its path to producing interferon today. In the early 1970's, scientists at the Massachusetts Institute of Technology sought to improve the beads by varying their chemical and physical properties. Beads were already being used in tissue culture but only certain kinds of cells would grow on them. The beads, which are made of dextran, a sugar polymer, offer two main advantages over traditional methods of tissue culture. First, they greatly increase the surface area for cell growth compared to the flat surface of bottles commonly used; the other, the cells' environment can be more easily controlled when a culture grows in suspension.

Unexpectedly, the MIT researchers found that the beads' charge density made a difference in cell growth. The phenomenon is still inexplicable, says William Thilly, one of the MIT scientists involved.

The university then took out a patent on the discovery and, after making overtures to several companies, awarded the exclusive license for manufacturing to Flow General.

Flow General has invested only $1 million to gear up for interferon production, a small financial risk for a company worth $78 million. Flow got by with little capital expenditure because it was already in the business of tissue culture. The firm develops cell lines to sell to other labs and manufactures media in which the tissues grow.

Victor G. Edy: Interferon maker

The small investment may pay off even if interferon does not prove to be the wonder drug for cancer, says Joseph E. Hall, president of Flow General and Flow Laboratories. The technological gains to make interferon may be carried over to produce other substances, including insulin and natural enzymes with medical use such as eurokinase, a kidney enzyme that is used to dissolve blood clots.

Although other companies have patents on making interferon, Hall says Flow is not interested in applying for one. The technology moves at such a rapid pace that a patent would be meaningless, he says.

Nevertheless, Flow is in intense competition with other manufactuers to produce interferon. Flow was awarded a $2 million contract this summer from the National Cancer Institute to produce interferon. NCI also signed two other contracts for 50 billion units each of leukocyte interferon. Warner-Lambert was awarded $900,000, and Meloy, a subsidiary of Revlon, received $989,000. The NCI is also negotiating with Burroughs-Wellcome to manufacture interferon from lymphoblastoid cells.

Other companies are making interferon through recombinant DNA techniques, but interferon from this method lacks a glycoside group which may or may not be a critical difference in the drug's possible efficacy. And whether one method of production is cheaper than another remains to be seen, Hall says.

The interferon produced for NCI by the various companies will be used in human trials to determine dosage levels and effectiveness.—MARJORIE SUN

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