Mixed welcome for genes on Wall Street

Genentech's interferon from yeast plasmid

Washington

Anybody interested in following the progress of interferon research may soon find it easier to refer to the pages of the *Wall Street Journal* than to look in the scientific literature. Last week, shares in the West Coast genetic engineering company Genentech Inc. rose $7, from $36 to $43, following the company's announcement that collaboration between Genentech and scientists at the University of Washington in Seattle had yielded interferon from genetically altered yeast cells. A few days earlier, shares in another publicly quoted company, Flow General, fell from 32 to 29⅜ cents with the news that the company faced delays in delivering the conventionally produced fibroblast interferon which it has agreed to supply to the National Cancer Institute for clinical trials.

The Genentech announcement was made during the First Annual Congress of Recombinant DNA Research, a privately sponsored meeting held in San Francisco. It represents the first public announcement of the successful use of yeast to produce mammalian proteins, although several other universities and companies are also working in the field and have yet to make their results known.

The techniques were developed by scientists in the University of Washington's genetics department, which has been studying the genetics of yeast since 1950. Dr Benjamin Hall, chairman of the department and one of the leaders of the research team, feels that the use of yeast could improve methods of producing interferon by up to a factor of ten.

Genentech has subsequently announced that it expects to be marketing interferon "before 1985". The company's vice-president, Mr Frederick Middleton, told a meeting of security analysts in San Francisco that the company's new human insulin, being developed with Eli Lilly and Co., would probably be on the market by the end of 1983. This would be followed within a year by human growth hormone, a bacterially produced version of which is now being tested on 20 children at the Great Ormond Street Hospital for Sick Children in London (see *Nature* 5 March, p.6).

Despite the long-term prospects, Mr Robert Swanson, the company's president, warned the analysts not to expect impressive performance figures from the company before it begins to market products. Citing the need for heavy investment in research and development, as well as clinical trials, Mr Swanson said that in the next 12 to 24 months "it mightn't be possible to show a profit on a quarter-to-quarter basis".

In contrast to its bullish reaction to Genentech's news about interferon production, Wall Street responded less kindly to the announcement from Flow General that the first delivery of human fibroblast interferon to the National Cancer Institute would be delayed because of contamination problems with the cells.

The company's biomedical subsidiary, Flow Laboratories, has signed a contract with the institute to provide 50,000 million units of fibroblast interferon — enough for 50,000 doses — using a technique invented and patented by the Massachusetts Institute of Technology in which the interferon-producing cells are grown on the surface of small charged spheres. According to a report issued by the company, the viability of scaled-up production using the so-called "superbeads" was demonstrated in December. Since then, however, contamination of the cells has resulted in a "setback of an indeterminate period" which will delay the deliveries to the institute, due this month, by "some weeks".

The institute is already sponsoring clinical trials at three centres using leukocyte interferon supplied by Meloy Laboratories of Springfield, Virginia, and at two centres with lymphoblast interferon produced by the Wellcome Foundation in London. It is also about to invite bids for the supply of gamma "immune" interferon for possible clinical trials, which has attractive properties distinct from the other more easily produced interferons. Flow General has reported that it is evaluating a process developed at New York University for the production of gamma interferon using conventional cell systems, to see if it would be able to produce sufficient quantities for further evaluation.

There is also evidence that the market's previous enthusiasm for genetic engineering stocks is waning. When the Berkeley-based Cetus Corporation went public last Friday, its shares opened at $23, fell to a low of $22⅞, and ended the day at $23⅛. Although this represented a record $119 million initial public stock offering for a new company on Wall Street, Cetus's debut was much less spectacular than that of Genentech, whose shares soared from $35 to $80 on the first day of trading, but have since dropped back to near their original price.

David Dickson

Benefits and snags of yeast plasmids

Until Genentech and the University of Washington, Seattle, announced their success with interferon, there had been little news, most of it gloomy, about the chances of expressing mammalian genes in yeast rather than bacteria. And this despite the establishment of at least one company, Collaborative Research Inc., specifically to exploit yeast. A consultant for Collaborative Research said last week that part of the problem was simply that not enough was known about the basic molecular biology of yeast to make easy its subversion for unnatural purposes.

One important setback for the advocates of yeast occurred early on, when it was discovered that yeast could not cope with split genes. Most mammalian genes have their coding sequences interrupted by non-coding, or intervening, sequences. Bacterial genes are not split in that way and, not surprisingly, bacteria do not possess the mechanisms to decode the information encoded in split genes. The hope was that yeasts, more highly evolved than bacteria, might possess split genes and therefore be able to cope with mammalian split genes. But this has not proved to be the case. Indeed, the overriding reason for the successful expression of the human interferon gene in yeast is because it is that human rarity — an unsplit gene.

Nevertheless, advocates of yeast still have reasons to be cheerful:

- Even split genes produce unsplit messenger RNA (the intermediary between the chromosome and machinery of protein synthesis in the cell) from which unsplit DNA, suitable for inserting into yeast, can be made with increasing ease.
- Inasmuch as there is some redundancy in the genetic code, yeast tends to share with mammals certain preferences of codon usage that are not favoured by bacteria; consequently yeast may find it easier than bacteria to decode mammalian genes.
- Yeast appears to have much the same ability as mammals to add carbohydrate groups to newly synthesized proteins, something bacteria cannot do; the carbohydrate groups may be essential for the activity of certain proteins.
- From at least the time that Bacchus sprang from the thigh of Zeus, there has been an accumulation of knowledge of the large scale culture of yeast. By comparison, bacterial culturing is still in its infancy, which perhaps explains the continuing problem of "phage-out", the disaster that befalls a bacterial culture when it is attacked by a bacterial phage or virus.

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