The idea that APP is a surface protein of general importance was reinforced by Brenda Shivers of the University of Heidelberg (F.R.G.). She and Peter Seeburg have recently cloned a cDNA encoding the rat equivalent of this protein, and showed that it is 97 percent homologous to the human counterpart. Moreover, its expression in rat is high in regions of the hippocampus that are only rarely seen to have plaques in human brain.

Gerry Higgins (Scripps Clinic, La Jolla, CA) reported very similar results concerning APP expression in human and monkey brains. This implies, Shivers said, that overproduction of APP is itself insufficient to lead to plaque formation, and that other factors common to SP-containing regions need to be sought.

Alpha₁-antichymotrypsin is also a component of SP. Perhaps the essential cofactor will turn out to be the serine protease inhibitor, alpha₁-antichymotrypsin (ACT). At a meeting of the American Academy of Neurology in April of 1987, Carmela Abraham and Huntington Potter (Harvard Medical School) reported that they had detected ACT as a second component of SP. In her presentation here, Abraham expanded and extended the story.

Using antibody probes against purified plaques, the scientists searched a λ gt11 liver-cDNA library and isolated a clone encoding a protein distinct from APP. A computer search using the deduced sequence revealed that it was identical to ACT. Antibodies to purified ACT bind to amyloid plaques from AD brain, confirming that the protease is indeed present in the deposits. Moreover, expression of ACT message is highest in those regions of the AD brain that are most affected by SP, low in regions which are normally spared plaque deposition, and almost undetectable in nondemented (control) brains. The next step, Abraham said, will be to determine whether the ACT protein that precipitates in the plaques is identical to the normal form of the protease inhibitor.

A number of models involving mutant or normal forms of the protein in altered processing of APP can be envisioned (see figure). A mutant protein, by analogy to prealbumin or cystatin C, could form filaments by itself, or allow abnormal release of β -amyloid from the membrane. And an excess of wild-type protein could contribute to plaque deposition by inhibiting an enzyme required for the normal degradation of β -amyloid.

—Harvey Bialy

QUARTERLY REPORT

BLACK MONDAY'S AFTERMATH

Compared to the water torture of 1983–84—when biotech stock prices trickled down to near invisibility—October's Black Monday was a tidal wave. In the aftermath, most of the biotech stocks found themselves soaked to the skin, trading 50 percent or more below their recent highs, many in the unmarginable zone below \$5 per share.

The cheap stock prices left stranded in Black Monday's wake also raised the possibility of major corporations in the drug and other industries trying to overtake small biotech companies. Investors and journalists have been keen to discuss the idea, and surely every investment banker worth his pinstripes must have commissioned a favorite bright-eyed young analyst to assemble a list of biotech companies, complete with calculations of cash and net value per share shown against a sorry-looking stock price. Some bankers may have even taken the opportunity to place a call with their favorite pharmaceutical company to further explore the idea.

But the idea makes little sense. Unfriendly takeovers are unlikely in biotechnology because most companies still consist mainly of so-called technological assets—a catch-all term that includes products under development, patents pending and issued, trade secrets, and last but not least the intangible value of the collective talents of a group of scientists and business people. Assets attached to tennis shoes that walk out of the building every evening are not likely targets of hostile takeovers.

The other option, of course, is a friendly acquisition. But the companies worth taking over are, by definition, the best ones in the group. Most of these, however, have managed to amass substantial amounts of capital and have little incentive to agree to an acquisition when their stocks are floundering near all-time lows. Needless to say, the negotiating picture would look very different if stock prices remain at current low levels for a couple of years.

Does all this mean that nothing could happen in terms of takeovers in the near term? Not quite. The top four or five biotechnology companies have sufficient "real" assets to attract suitors. Perhaps a foreign or non-drug company could be moved to launch a tender offer. More likely, however, is the possibility that a corporation with long-term acquisition plans may take advantage of the current low prices and establish a solid 10–20-percent equity position. Such a move, aptly termed a "bear hug" by PaineWebber biotech analyst Linda Miller, could facilitate a future acquisition effort and preempt others from pursuing the same target. If nothing else, a fair gain is likely to be realized in the stock.

In light of the excessively depressed stock prices, many companies have considered buying back some of their outstanding equity. But working capital remains valued and scarce, so the decision of R&D-intensive biotech companies to trade this key resource for stock does not appear to make much sense. One innovative biotech executive proposed an intriguing solution to the dilemma: Rather than buying their own stock back, biotech companies ought to buy the stock of their closest respected competitor and hold it until prices rally. Thus a biotech company could benefit from the sector's weakness without resorting to purchasing its own stock. It might have proved a tall order, however, to convince Amgen to buy stock in Genetics Institute, or Immunex to invest in Cetus.

Amidst the irreverent ebb and flow of the last few weeks, reason was articulated best by Amgen president George Rathmann, who recalled a statement made by Bill Bowes, a noted venture capitalist and a founder of Amgen. During a 1984 Amgen board meeting when the same issue of stock buybacks came up, Bowes opined: "Biotech companies may run out of cash, but they never run out of stock."

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