FINANCING

BIOTECH START-UPS TURN TO THE PUBLIC—AGAIN

NEW YORK—Initial public offerings (IPOs) are the order of the day for biotechnology companies. "It's 1983 revisited," says Steven Zimmer, vice president of Eberstadt-Fleming (New York, NY). "The window is wide open and all the companies are filing. And that's what they should be doing."

The largest, and perhaps most eagerly awaited, IPO comes from Genetics Institute (Cambridge, MA). By selling 1.75 million shares at \$25–28 each, the company hopes to raise almost \$50 million. With 10.5 million shares outstanding after the offering, the firm's market capitalization will stand at \$260–290 million.

Other recent or expected filings include issues by T Cell Sciences (Cambridge, MA), Oncogene Sciences (Mineola, NY), Genzyme (Boston, MA), Repligen (Boston, MA), Biotherapeutics (Franklin, TN), Ingene (Santa Monica, CA), Hana Biologics (Berkeley, CA), Xoma Corp. (San Francisco, CA), and Synergen (Boulder, CO). Reportedly, both the Liposome Company (Princeton, NJ) and NPI (formerly Native Plants Inc., Salt Lake City, UT) are also close to registering with the Securities and Exchange Commission to go public. And more are expected to follow should the market for such fundraising remain receptive. In fact, the running joke around biotech circles says that the president of any private biotech company who claims he's not

considering taking the public plunge is either stupid or lying. (And not too many of them are stupid.)

One difference that Zimmer sees from the last IPO binge in 1983 is that the companies going public today tend to be highly focused in their strategy. The exceptions to this trend, he notes, include broad-based gene-splicers Genetics Institute, Repligen, and Synergen. Zimmer adds that in a bull market such as this one, the early IPOs may do well; later ones could have trouble as the window starts to close.

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Linda Miller, biotechnology analyst for PaineWebber (New York, NY), reports that approximately \$450 million in public funds have been channeled into biotechnology companies so far this year, including secondary

stock offerings from companies like Amgen, Centocor, and Immunex. About \$150 million in public funding—mostly IPOs—has been announced but is yet to be raised.

"I don't think that at this point you can play the IPOs like in '83," she says, referring to the period in which all IPO stocks increased in value when they were first offered. "Now you have to look at these companies as long-term situations."

Miller views the firms going public now as more mature than many in 1983. Xoma, for example, is sponsoring clinical trials with its monoclonal antibody-toxin conjugates, and Repligen has some important contracts, including one with Gillette. Miller adds that the valuations attached to the Wall Street newcomers are comparable to those found in 1983. But since interest rates are about one-third of their 1983 levels—and with Genentech's current market value in the stratosphere at over \$2.5 billion—these stocks are cheaper in a relative sense.

Miller regards the period between 1984 and the beginning of 1985 as a time in which investors distinguished between biotech success stories and the also-rans. Now, she says, investors will have a chance to do the same thing for a whole new set of companies and technologies. But this new opportunity for profit, of course, comes with new risks.

—Arthur Klausner

WAKSMAN INSTITUTE-BIO/TECHNOLOGY CONFERENCE

A 'NEGATIVE ENHANCER' CONTROLS β -INTERFERON

NEW BRUNSWICK, N.J.—The enhancer element of the β -interferon gene contains negative regulatory sequences. This novel result was reported by Tom Maniatis (Harvard University) speaking at the Third Waksman Institute-Bio/Technology Colloquium held here in April.

Maniatis described a series of experiments, done in collaboration with Stephen Goodbourn and Hal Burnstein, that show the β -interferon gene regulatory element (IRE) contains two functional regions. Deletion of 19 bases from the 3' end of the IRE (-77 to -36) results in a large increase in the level of interferon mRNA in the absence of inducer, suggesting that this region contains negative control sequences. The remaining sequences at the 5' end of the element behave like a classical enhancer, increasing transcription levels in either orienta-

tion and independent of position.

Comparison of these 5' sequences with other enhancers shows striking homologies. The region between -76 and -67 very closely matches E1a enhancer elements of adenoviruses 5 and 7, the polyoma enhancer, and the human HSP70 promoter. It is likely, Maniatis said, that these transcription elements are recognized by common factors, but in the case of IRE their binding is blocked by a protein bound to the negative regulatory end.

When the IRE is placed immediately adjacent to a fusion construct—consisting of the TK promoter joined to the β -interferon structural gene on a bovine papilloma virus plasmid—a dramatic decrease in the basal level of interferon-mRNA is seen. The negative effect is relieved when cells containing the plasmid are treated with an interferon inducer.

In vivo DNase footprinting analysis of the human β -interferon 5' flanking region gives additional support to the idea that the negative regulatory sequence is the binding site of a repressor. The analysis shows that a factor bound to the element in uninduced cells dissociates upon induction, and is followed by the binding of another protein to the region of the IRE that includes the constitutive transcription element.

Maniatis speculated that the negative control mechanism he proposes for the β -interferon element may apply to other regulated enhancers. He cited recent reports that factors binding specifically to the immunoglobulin heavy chain gene enhancer are present in extracts of both B cells and HeLa cells, and that the adeno E1a protein can inhibit the activities of viral enhancers.

—Harvey Bialy