"A TECHNOLOGY OF LAST RESORT"

FEW FIRMS PURSUE ANTI-IDS

NEW YORK—Biotechnology companies are no longer limited to genetic engineering and monoclonal antibody technology. Indeed, scores of biotech companies are currently developing newer technologies like gene therapy, oligonucleotide therapy, and rational drug design.

Of these newer technologies, perhaps the least pursued is anti-idiotypic monoclonal antibody technology, a technique generally used to make therapeutic vaccines. Only three U.S. biotech companies—all of which went public last year—are pursuing anti-idiotypic technology, including Idec Pharmaceuticals (La Jolla, CA), ImClone Systems (New York), and Epigen (Boston, MA). "Anti-id technology is a technology of last resort," says Samuel Waksal, ImClone's president and chief executive officer. "It's only useful when other approaches aren't readily available."

An anti-idiotypic monoclonal acts as a surrogate antigen. It is made by making a monoclonal to a monoclonal. Since the binding site of the first monoclonal is specific to an antigen, the binding site of the second monoclonal mimics that antigen. As a vaccine, an anti-idiotypic antibody is useful when the mimicked antigen doesn't naturally elicit a strong immune response because it's too small or too similar to self. An anti-idiotypic antibody, on the other hand, particularly one of mouse origin, elicits a strong immune response. An anti-idiotypic antibody is also useful when a mimicked antigen can't readily be produced in commercial quantities, because it's a glycolipid, for instance. Using monoclonal antibody technology, companies can readily make commercial quantities of anti-idiotypic antibodies.

Idec

Idec is the leading anti-id company. A loser of $5.7 million last year, Idec raised $45 million in its 1991 initial public offering (IPO). It currently has four anti-ids in clinical trials.

Idec's lead product is an exception, as it's not a vaccine. A panel of 14 anti-idiotypic antibodies, the product is in initial phase III trials for low-grade non-Hodgkin's B-cell lymphoma, a cancer that afflicts some 150,000 people in the U.S. Idec chose an anti-idiotypic approach because each antibody-producing B-cell expresses a unique antibody on its surface. Ideally, an anti-idiotypic antibody specific for the antibody of a malignant B-cell would knock out that B-cell, while leaving normal B-cells unaffected. Idec, in fact, has seen tumor shrinkage in 10 of 16 evaluable patients treated with its anti-id panel, with few side effects. Yet it doesn't know precisely how anti-id/antibody binding kills malignant B-cells.

In aggregate, Idec's 14 anti-idiotypic antibodies bind to 25 percent of B-cell lymphomas. Idec screens the tumors of B-cell lymphoma patients *in vitro* for reactivity with its panel of anti-idiotypic antibodies. If the company finds a match, it treats the patient with the single reactive antibody. That its antibodies are murine is of little concern, says Idec, since lymphoma patients—because their B-cells are damaged—show little antibody response to mouse monoclonals.

The product faces hurdles. Before granting it marketing approval, the Food and Drug Administration (Bethesda, MD) might "decide to regard the 14 antibodies in the plural rather than the singular and require a separate clinical trial for each," says David Webber, an analyst at Alex Brown & Sons (New York). He adds, though, that the antibodies's "structural similarity and identical manufacturing process suggests that this is unlikely."

Another hurdle is the huge amount of product needed to treat patients. Each patient will need about 6 grams of antibody, a gargantuan amount compared to the milligram quantities needed to treat patients with anti-idiotypic vaccines. Such large doses undoubtedly contribute to the astronomical price of $12,000 per patient projected for the product.

Idec owns North American marketing rights to the antibody panel. Boehringer Ingelheim (Ingelheim am Rhein, Germany)—which will make the antibodies because it has excessive manufacturing capacity—will market the product in Europe, while Zenyaku Kogyo (Tokyo) and the Institute of Immunology (Tokyo) will sell it in Japan and Asia. Alex Brown's Webber believes the product will reach the U.S. market in 1995, generating $40 million in sales and making Idec profitable that year.

Idec's other three anti-ids in clinical studies are therapeutic vaccines.

- Two anti-idiotypic antibodies are in phase I/II studies for malignant melanoma, a skin cancer that will strike 33,000 people in the U.S. this year. Idec has shown that the murine products—which mimic melanoma antigens—stimulate antibody-based immunity. It is unsure whether they stimulate cellular immunity.
- An anti-idiotypic antibody is in phase I trials to slow the onset of AIDS in HIV infection. The murine antibody mimics the CD4 binding region of gp120, an HIV coat protein, says Idec.

Anti-id Pipeline

Product	Indication	Status
	Idec Pharmaceuticals	
Specifid	B-cell lymphoma	Phase III
I-Mel-1	Malignant melanoma	Phase I/II
I-Mel-2	Malignant melanoma	Phase I/II
3C9	HIV infection	Phase I
	ImClone Systems	
BEC-2	Malignant melanoma	Phase I
	Epigen	
Unnamed	Carcinoma	Research

Source: Idec Pharmaceuticals, ImClone Systems, and Epigen

ImClone and Epigen

For its part, ImClone has one anti-id—a therapeutic melanoma vaccine—in clinical trials. The company, which lost $10.6 million in fiscal 1992, raised $35 million in its 1991 IPO.

ImClone's melanoma vaccine—a murine surrogate for a glycolipid called G_{D3}—is in phase I trials and has stimulated antibody-based immunity in some patients. E. Merck (Darmstadt, Germany) owns marketing rights to the vaccine in Europe, New Zealand, and Australia, while ImClone plans to manufacture and market the product in the U.S. Denise Gilbert, an analyst at Smith Barney (San Francisco, CA), sees the vaccine reaching the U.S. market in 1996. At a cost of $2,000 per patient, it should help ImClone reach profitability in 1988 by generating $43 million in sales, says Gilbert.

Epigen has just begun working on a therapeutic anti-id vaccine to treat carcinomas, the solid cancers that make up 84 percent of the 1.1 million new cancers diagnosed in the U.S. each year. A loser of $1.3 million last year, Epigen raised $5.2 million in its 1991 IPO.

To make its anti-id, Epigen will make a murine monoclonal to its EPN-141 murine monoclonal, which is specific for the human carcinoma antigen, a glycoprotein on the surface of carcinomas. Though Epigen hasn't decided what carcinoma it will target first, it optimistically expects to start vaccine clinical trials next year.

Perhaps Idec and ImClone are also optimistic. "Anti-id technology is complicated," says a biotech executive. "Each of the technology's many steps increases the chance of error."

—B.J. Spalding