

CORPORATE STRATEGY

APPLYING TODAY'S BIOTECHNOLOGIES

BALTIMORE, Md.-While biotechnologies are accelerating the pace with which we can elucidate disease mechanisms, few biotech companies have a shot at becoming fully integrated pharmaceutical companies. They can do so only if their products are originals-not "replacement therapies"-and can be sold into a welldefined market. On the other side of the coin, despite increasing economies of scale resulting from the big company/big company mergers of the past year, even the pharmaceutical giants must narrow their focus and concentrate on only a handful of disease states in order to achieve "critical mass." These daunting messages formed the cornerstone for the Alex. Brown & Sons (Baltimore, MD) Fifteenth Annual Health Care Seminar, held here the second week in May. What they signaled to biotech investors is: Watch out. The Big Boys are watching and waiting.

What's changed, says David Webber, Alex. Brown's biotech analyst, is



the recognition of the centrality of these technologies and their power over the coming decades. He points out that "we're way past the 'window on technology' approach taken in the past by companies such as Eli Lilly (Indianapolis, IN)." Webber cites the recent collaboration between Synergen (Boulder, CO) and Hoffmann La-Roche (Basel, Switzerland) on interleukin-1 receptor antagonist proteins as illustrative of the way the large companies now use biotechnologies to identify a lead compound.

"The insights [between the companies] feed back and forth in terms of disease mechanism and information from clinical trials on the use of the protein." Then, they turn to their internal R&D capabilities to develop small-molecule oral mimics as drug candidates. He warns against underestimating the speed with which these mimics will come to the forefront. "There are obvious attractions for folding this all back into medicinal chemistry...Small-molecule mimics



Neuraminidase Isozyme S cleaves $(\alpha, 2\rightarrow 3)$, $(\alpha, 2\rightarrow 6)$ and $(\alpha, 2\rightarrow 8)$ linkages of N-acetylneuraminic acid in glycoconjugates. In the absence of detergents and calcium ion, the isozyme S hydrolyzes N-acetylneuraminyl moiety of polysialogangliosides and produces monosialoganglioside G_{M1} , while in the presence of detergents G_{M1} is further desialylated to asialoganglioside G_{A1} .

The character is similar to <u>Vibrio</u> cholerae neuraminidase except requirement of Ca^{2+} in the latter.

Origin	: From <u>Arthrobacter</u> <u>ureafaciens</u>
Activity	: More than 80 units/mg-protein for N-acetylneuraminyllactose (NAN-lac) More than 20 units/mg-protein for bovine submaxillary mucin More than 40 units/mg-protein for colominic acid More than 60 units/mg-protein for bovine brain ganglioside
Properties	: Molecular weight; approx. 52,000 (gel filtration, SDS-PAGE) Optimum pH ; 3.8-4.4 (for bovine brain ganglioside) pH stability ; 3.5-10.0 Thermal stability; below 60°C (pH 4.0, 20min)

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are still in a young phase relative to recombinant technology, which has 20 years of history."

Yet Webber does not downplay the continuing role of the smaller companies. "There will always be cultural issues, and the big companies remain dominated by chemists, who look down on biology as 'messy.' " As well, the concept of achieving critical mass is size-dependent. "You can view critical mass in a number of ways--it's quality and quantity," says Webber. "Small companies may be able to maintain it by being more focused, more entrepreneurial..the criticalmass problem doesn't come up until the commercialization phase." That freedom from inertia will be pivotal in enabling them to maneuver more adroitly over the rapidly changing terrain.

Nor does Webber think the industry will turn back to synthetic chemicals exclusively. "Genetics Institute, for example, has a rational drug design program, but one of its basic premises is that there are thousands of proteins in the body, and we only know about 100 or so...We will continue to mine the body for proteins with therapeutic use."

A recent Alex. Brown report on biotechnology's role in the life sciences notes that the business environment now offers more creative avenues for biopharmaceutical firms to generate returns for investors. Yet it also cautions that "Solo commercialization strategies will be largely limited to products that address concentrated markets, such as erythropoietin for kidney-dialysis patients. Products for more diffuse markets will often require strategic alliances to exploit the commercial experience and infrastructure of larger companies."

Within the pharmaceutical group, too, globalization of resources and markets means that new entrants must continue to seek scale and outside collaborators. Thus, says Alex. Brown pharmaceutical analysts Adele Haley and Richard Stover, consolidation is a misnomer. Instead, concentration should be the key word to describe the current climate. They point to the fact that companies such as Eastman Kodak (Rochester, NY), Monsanto (St. Louis, MO), and Dow Chemical (Midland, MI) have been targeting the life sciences and divesting unrelated businesses to concentrate their resources within the life sciences.

-Mark Ratner