Barriers to Alzheimer Disease Drug Discovery and Development in the Biotechnology Industry

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Summary: The major barrier to Alzheimer disease (AD) drug discovery and development in the biotechnology industry is scale. Most biotechnology companies do not have the personnel or expertise to carry a drug from the bench to the market. Much effort in the industry has been directed toward the elucidation of molecular mechanisms of AD and the identification of new targets. Advances in biotechnology have generated new insights into disease mechanisms, increased the number of lead compounds, and accelerated biologic screening. The majority of costs associated with drug development are in clinical testing and development activities, many of which are driven by regulatory issues. For most biotechnology companies, the costs of such trials and the infrastructure necessary to support them are prohibitive. Another significant barrier is the definition of therapeutic benefit for AD drugs; Food and Drug Administration (FDA) precedent has established that a drug must show superiority to placebo on a performance-based test of cognition and a measure of global clinical function. This restrictive definition is biased toward drugs that enhance performance on memory-based tests. Newer AD drugs are targeted toward slowing disease progression; however, there is currently no accepted definition of what constitutes efficacy in disease progression. Despite these obstacles, the biotechnology industry has much to offer AD drug discovery and development. Biotechnology firms have already developed essential technology for AD drug development and will continue to do so. Biotechnology companies can move more quickly; of course, the trick is to move quickly in the right direction. Speed may offset some of the problems associated with lack of scale. Additionally, biotechnology companies can afford to address markets that may be too restricted for larger pharmaceutical companies. This advantage will have increasing importance, as therapies are developed to address subtypes of AD.

Key Words: Alzheimer disease—Drug development—Biotechnology.

The major barrier to Alzheimer disease (AD) drug discovery and development in the biotechnology industry is scale. A few definitions are appropriate in framing the role of biotechnology in AD drug development. First, pharmaceutical companies are involved in basic research, lead development, clinical testing, drug manufacture, and product marketing. Thus, by these criteria, most biotechnology companies are not pharmaceutical companies. The majority of biotechnology companies are in business to provide enabling technologies for drug discovery and development. A limited list of examples is provided in Table 1.

Much of the effort of the biotechnology industry and academic research has been directed toward the elucidation of molecular mechanisms of disease and subsequent identification of new targets (Sparks et al., 2000; Sramek and Cutler, 1997). The explosive advances in biotechnology have generated new insights into disease mechanisms, vastly increased the number of lead compounds available for subsequent development, and accelerated
biologic screening. In the aggregate, these technologies have already significantly increased the pace of drug development. Recombinant DNA technology, transgenic animal constructs, combinatorial chemistry, and high-throughput screening technologies are now firmly entrenched in the industry (Price et al., 1998; Loring et al., 1996; Sommer et al., 2000; Floyd et al., 1999; Drews, 2000; Browne et al., 1995; Spence, 1999; Kubinyi, 1995; Kaul, 1998; Rudmann and Durham, 1999). Functional genomics and proteomics are rapidly being adopted (Steiner and Anderson, 2000; Ohlstein et al., 2000; Dehouck and Metcalf, 2000).

However, most biotechnology companies are focused on one or a few innovative technologies, and each of these is a major investment that may represent the majority of a company’s assets. As a result, there is considerable risk involved in any choice of technologic platform. This risk is compounded when potential therapeutic applications are limited to a single disease; the wrong choice can be a major setback for a small company.

The majority of costs associated with drug development are involved in clinical testing (28.3%), and an additional 44.6% of costs are allocated to development activities, many of which are driven by regulatory issues (Fig. 1). The complexity of these “non-scientific” activities is often ignored or undervalued by biotechnology companies. However, these activities are a core industry competence for drug development. Most biotechnology companies do not have the expertise required to execute all these crucial activities. In addition, biotech corporate culture often does not value the skills of experts in these essential areas.

Estimates of success from laboratory to market vary, but one commonly quoted figure is 1 in 5,000 new chemical entities survive until market (Heilman, 1995). If all molecules derived from a combinatorial screen are considered, this number may approach 1 in $10^6$. As a result, the relative value of an individual molecule is rather small in the initial stages of discovery research, and significant value is only added at successive stages after discovery and during clinical development. Thus, technology-based companies without development expertise sell relatively high-cost, low-value commodities rather than pharmaceuticals.

For AD, Food and Drug Administration (FDA) precedent has established that a drug must show superiority to placebo on a performance-based test of cognition and a measure of global clinical function. Drugs must also be demonstrated to be safe in the AD patient population. In addition, studies are necessary to assess drug interactions, measure impact of the drug on other disease symptoms, and assess efficacy compared with and in combination with other drugs. These programs take 4–5 years to complete, and costs may exceed $100 million (Heilman, 1995; Schacter et al., 1992). The probability of success varies with each type of compound but is often less than 20% for a compound in initial phases of clinical testing. For most biotechnology companies, the cost of a clinical trial and the investment in infrastructure necessary to support a clinical program are prohibitive.

A significant barrier to AD drug development is the definition of therapeutic benefit for AD drugs; FDA precedent has established that a drug must show superiority to placebo on a performance-based test of cognition and a measure of global clinical function. The most commonly accepted instrument used to test cognitive performance is the Alzheimer’s Disease Assessment Scale, Cognitive Portion (ADAS-cog) (Doraiswamy et al., 1997). A variety of global clinical assessment tools are

<p>| TABLE 1. |</p>
<table>
<thead>
<tr>
<th>Technology</th>
<th>Target</th>
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<tr>
<td>Genomics</td>
<td>Therapeutic targets, diagnostics, prediction of therapeutic outcomes</td>
</tr>
<tr>
<td>Proteomics</td>
<td>Therapeutic targets, rational drug design</td>
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<tr>
<td>Combinatorial chemistry</td>
<td>Drug identification</td>
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<tr>
<td>Biological combinatorial chemistry, phage display</td>
<td>Drug identification</td>
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<tr>
<td>Drug delivery systems</td>
<td>Delivery of new drugs, improved delivery of existing compounds</td>
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<td>Transgenic animal constructs</td>
<td>Drug screening</td>
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<tr>
<td>Recombinant DNA methods</td>
<td>Therapeutic targets, drug identification, drug manufacture, diagnostics</td>
</tr>
<tr>
<td>Novel screening methods</td>
<td>Target and drug identification</td>
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FIG. 1. Cost allocation of drug development (from Pharmaceutical Manufacturers of America 2000).
The current definition of biotechnology, which is often slow and less than conclusive. There is a considerable time lag between decisions and their implementation. In addition, all programs have to be balanced against a corporate portfolio of obligations and opportunities. In smaller companies, decisions—for better or worse—are made more quickly; speed in development may offset some of the problems associated with lack of scale.

Biosciences companies can afford to address small markets. Large pharmaceutical companies need to develop drugs for large patient populations. As a result, there is a bias toward strategies that target relatively advanced stages of diseases, thereby maximizing potential markets. Biotechnology can afford to address specific aspects of a disease and focus on smaller markets that would be ignored by larger companies. Given the potential size of the AD market (Fratiglioni et al., 1999), this difference may not seem to be an issue, but it will become important in AD. In addition to relatively rare cases of autosomal dominant disease caused by APP and presenilin mutations (Cruts and van Broeckhoven, 1998; Gantier et al., 1999; Campion et al., 1999), numerous genes have been implicated in the development of AD. The best known of these is APOE (Cruts and van Broeckhoven, 1998; Marin et al., 1998; Li et al., 1996); however, more than 20 additional genes have been implicated in AD. Although some of these findings may turn out to be statistical artifacts, these results indicate that AD is probably a syndrome with a final common pathologic endpoint. As a result, there are doubtless several unexplored therapeutic approaches that may target...
subtypes of AD. In the future, it is likely that AD, like most complex common diseases such as cancer, hypertension, and heart disease, will be managed with a variety of medications. The development of tests with sufficient predictive value to individualize therapy will greatly expand these efforts. Although the market for drugs that target subtypes of AD may initially be small, their impact on a small company’s valuation can be substantial.

Biotechnology companies will continue to make major contributions to AD drug development. However, the potential for biotechnology companies to rapidly launch AD drugs will depend, in large part, on their ability to evolve into small, integrated pharmaceutical companies. Maximizing growth while maintaining focus presents several difficult and complex issues. Nevertheless, these small pharmaceutical companies are uniquely positioned to provide enabling technologies for drug development and breakthrough pharmaceuticals for AD patients.

REFERENCES


