Commentary

Barriers to Drug Discovery and Development for Alzheimer Disease


Summary: Alzheimer disease (AD) is a neurodegenerative condition leading to progressive, irreversible loss of cognitive and behavioral function. Despite considerable investments in neuroscience research, only four drugs, all cholinesterase inhibitors, have been approved for the symptomatic management of AD in the United States. Although basically safe and modestly effective, these drugs are far from ideal, being neither universally efficacious nor disease modifying. AD exacts a considerable toll in direct medical costs, quality of life, and caregiver burden for persons and society. In addition to the obvious clinical benefit, therapeutic agents for AD and related dementias represent a considerable market opportunity for the pharmaceutical and biotechnology industries. There are currently 8–10 million AD sufferers in the seven major pharmaceutical markets. The market will grow rapidly in coming decades, as the developed world experiences an enormous increase in its elderly population. Given the great need for new therapeutic agents to manage and prevent AD, the Institute for the Study of Aging and the Fidelity Foundation organized a workshop, “Barriers to the Discovery and Development of Drugs for Alzheimer’s Disease,” to examine ways to expedite drug discovery and development. The identified barriers and potential solutions will be discussed here and in the accompanying articles in more detail. Key Words: Drug discovery—Drug development—Aging—Dementia—Alzheimer disease.

Alzheimer disease (AD) is a neurodegenerative disease causing progressive, irreversible loss of cognitive and behavioral function (Carr et al., 1997). Almost a century has gone by since the first description of AD, and 30 years have passed since the recognition that AD is the most common cause of dementia in the elderly population (Fratiglioni et al., 1999; Edelberg and Wei, 1996; Breteler et al., 1995). Unfortunately, despite considerable investments in neuroscience research cumulatively amounting to billions of dollars over the past three decades, only four drugs, all in the same class of cholinesterase inhibitors, have been approved for the symptomatic management of AD in the United States (Taylor, 1998). Although basically safe and modestly effective in improving cognitive and daily function in some patients, these drugs are far from ideal, being neither universally efficacious nor disease modifying. For AD sufferers and their caregivers, there is still no cure or an effective therapeutic agent to prevent or slow the progression of the disease.
Alzheimer disease exacts a considerable toll in direct medical costs, quality of life, and caregiver burden for persons and society; it is considered the third most costly disease after heart disease and cancer, costing about $100 billion per year in the United States alone in direct and indirect costs (Fillit, 2000; Meek et al., 1998). The cost effectiveness of AD therapeutic agents has only recently begun to be investigated because of the recent availability of these drugs (Knapp et al., 1998; Trabucchi, 1999; Schumock, 1998; Ernst and Hay, 1997). Initial studies indicate that these modestly effective AD therapeutic drugs are cost effective (Hauber et al., 2000; Fillit et al., 1999; Neumann et al., 1999; Jonsson et al., 1999; Stewart et al., 1998; Henke and Burchmore, 1997).

In addition to the obvious potential for clinical benefit, therapeutic agents for AD and related dementias represent a considerable market opportunity for the pharmaceutical and biotechnology industries. About 5–10% of persons aged 65 years or more will suffer from the disease, and up to 40% of persons aged 80 years or more, the most rapidly growing population segment in the developed world, will suffer from AD (Brookmeyer et al., 1998; Hebert et al., 1995; McGee and Brayne, 1998). There are currently 8–10 million AD sufferers in the seven major pharmaceutical markets (United States, France, Germany, Italy, Spain, United Kingdom, and Japan).

The market for AD therapeutic agents will grow rapidly in the coming decades, as most of the developed world will experience an enormous increase in its elderly population as the “baby boomers” reach age 65 years (Cormran, 1996; Kennedy, 1998; Brookmeyer et al., 1998). Add to this opportunity the fact that the majority of new cases of AD worldwide will come from the developing world, including China, India, and other regions, and the worldwide market expands even more. For example, in India, although only 6% of its one billion people are aged 65 years or more, this population group represents 60 million people, compared with about 35 million people aged more than 65 years in the United States.

Sales of the currently available AD therapeutic agents are already approaching $1 billion in the United States, with about 60% of known AD sufferers getting at least a “start” on an AD therapeutic medication. However, long-term compliance remains an issue, with an average term of usage of about 120 days despite recent data suggesting the cholinesterase inhibitors are effective at least up to 1 year. Additionally, the market for drugs for AD will likely expand in the near future to include persons with mild cognitive impairment (MCI), thought to be a precursor to AD, with a conversion rate of about 15% per year or 50% at 3 years (Almkvist et al., 1998; Petersen et al., 1987; Petersen, 2000). Inclusion of MCI would increase the number of potential persons eligible for treatment by three- to fivefold, as there are 14 million persons with MCI in the United States. The potential to add patients with age-associated memory impairment (AAMI) (Forstl et al., 1995) would increase the market further.

Given the great need for new therapeutic agents to manage and prevent AD, the Institute for the Study of Aging and the Fidelity Foundation organized a workshop, “Barriers to the Discovery and Development of Drugs for Alzheimer’s Disease,” to examine ways to expedite drug discovery and drug development. Invited participants included experts in AD research from the pharmaceutical and biotechnology industries, industry-related consulting firms, and academia. The panel identified barriers to new drug discovery and development for AD and made recommendations accordingly. These and other barriers and potential solutions will be discussed here and in the accompanying articles in more detail.

LACK OF VALIDATED TARGETS

Alzheimer disease is considered a clinical-pathologic syndrome. Although generally reliable, the clinical diagnosis of AD requires documentation of progressive deficits in memory and evidence of other global cognitive disturbances in domains such as language, learned motor behaviors, and executive functioning (planning and organizing). “Absolute” diagnosis can only be made from post mortem brain tissue with the identification of plaques and tangles, and there are no reliable or definitive laboratory tests.

Most scientists consider AD a multifactorial clinical-pathologic syndrome, with several potential genetic (such as apolipoprotein E) and environmental (such as head trauma) risk factors (Tang et al., 1996; Nicoll et al., 1996). As a result, several hypotheses have been generated for the development of new therapeutic agents that address risk factors (such as high cholesterol or hypertension) as a means of prevention or mechanisms related to final common pathways of pathogenesis (such as oxidation or inflammation) (Sparks, 1997; Sramek and Cutler, 1999; Sparks et al., 2000; Drachman and Leber, 1997; Akiyama et al., 2000). Few primary etiologic mechanisms, such as anti–β-amyloid strategies, have been tested and clinically validated, although promising approaches to reducing β-amyloid accumulation in the brain are currently in various phases of preclinical or early clinical (proof-of-concept) testing (Sramek and Cutler, 1999; Verbeek et al., 1997). Nevertheless, because of the likely multifactorial nature of the disease,
the response to any approach or medication may be limited and depend on particular factors in subgroups of patients.

Despite decades of research, there remains a lack of validated therapeutic targets, presumably stemming from our incomplete understanding of the pathogenesis of the disease (Selkoe, 1991). Overcoming this ignorance barrier will ultimately require more fundamental neuroscience and clinical research and attracting the best and the brightest scientists and clinicians to AD research.

Nevertheless, development and testing of new, potential therapeutic targets could be initiated now. As loss of neurons and their connections is thought to ultimately result in impaired cognitive function, identifying specific pathways of neurodegeneration in AD patients would represent valuable therapeutic targets for new drugs. Investment in biochemical and cell-based high throughput screening assays using “less validated targets” that may identify new compounds can be initiated; for example, compounds capable of preventing neurofibrillary tangle formation, β-amyloid accumulation, oxidation of neuronal proteins, mitochondrial deficits, restoration of calcium homeostasis, or of enhancing regeneration of lost brain cells and their connections could be identified. The application of new technologies, such as genomics and proteomics, to AD drug discovery will play an important role.

In addition, the past 20 years of AD research have created many hypotheses of pathogenesis that can now be tested in clinical trials, such as antiamyloid strategies, antiinflammatory strategies, neurotrophins, neuroprotectants, and more recently, strategies directed toward normalizing cholesterol metabolism, controlling hypertension, homocysteine levels, diabetes, and others (Sramek and Cutler, 1999). Some of these approaches are now in clinical trials; however, such trials are risky and expensive. Nevertheless, investment in more clinical trials is needed now, rather than a “wait and see” attitude toward the revelation of some “fundamental” cause of AD, as the multifactorial nature of the illness is more generally recognized.

**Recommendations**

New drug discovery and drug development research for AD as described is risky and expensive. Academia, industry, philanthropic organizations, and government must recognize the opportunity presented and begin to place more emphasis and priority on funding translational research in AD. Investors with a commitment to AD should be willing to take increased risks and fund small biotechnology companies to test new, high-risk therapeutic approaches. This support will help develop an infrastructure that will attract more investment and prepare the field for the explosion in new AD cases we expect to occur in the next few years.

**LACK OF ANIMAL MODELS**

Despite some recent progress, there remains a lack of animal models that clearly reflect the disease state and include all of the clinical and pathologic features of the disease (Loring et al., 1996; Price et al., 1998; Sommer et al., 2000). None of the current models or modeling systems provides the full spectrum of neurobiologic and clinical aspects of the disease. Nevertheless, some recent models are closer to the human disease and have proven useful for studying β-amyloid production and deposition. Animal models have shaped the history of drug discovery and development in other fields; for example, in the discovery of antiepileptic drugs, animal seizure models that successfully predicted human efficacy led to rapid advances. The same would likely be true in AD research; better animal models are clearly needed.

Perhaps as important is the problem of access to models. In many cases, current animal models of AD are not freely available for use in research and for drug screening and preclinical development because of intellectual property and licensing issues. Many animal models of AD belong to academic institutions and corporations and are protected by patents. When available, they have been costly and their use restricted. The high costs of these models are generally prohibitive to academic scientists and small biotechnology companies, whereas licensing issues make their use by industry limited.

**Recommendations**

Philanthropic organizations and government bodies should help to overcome these difficulties by providing resources and funding to make existing animal models more affordable and available; current efforts in this regard are inadequate. As many of the animal models developed to date have been developed with government and philanthropic funding, it is time for new models of funding that ensure public availability of animal models on a much less restricted basis, while still recognizing the intellectual property rights of inventors. New forms of grant agreements should be implemented that adequately reward investigators and their institutions, while ensuring wider availability of new animal models. US tax law requires that findings from research funded by tax-exempt dollars be made available to the public in a reasonable fashion. The Bayh-Dole Act of 1980 gives title to inventions made with federal money to the universities and requires them to exploit them for the public good.
typically by patenting and licensing the invention. Some institutions appear to be in danger of pricing AD animal models so highly that they may do the public a disservice by preventing or restricting AD research with those models. Government and philanthropic organizations could also spur research by supporting the creation of AD animal model repositories that systematically review existing models, negotiate licenses to distribute models to academic researchers, and support the cost of establishing and maintaining colonies of aging animals. Government and philanthropic organizations should also invest in a systematic, large-scale effort to develop new animal models that more closely resemble AD and ensure that these models are readily available.

**BARRIERS IN THE DESIGN AND IMPLEMENTATION OF CLINICAL TRIALS**

Clinical trials are an issue that affects pharmaceutical and biotechnology companies alike; new designs are needed for AD trials, particularly risky and expensive prevention trials. The long duration trials that will likely be needed to demonstrate an effect on AD disease progression will be extremely costly and difficult to justify strictly on the basis of preclinical or epidemiologic research. Early-phase, proof-of-concept trials are needed to support moving forward with an expensive, long duration trial.

Better clinical trial designs to increase the efficiency of the process are needed. Presently, a 6- to 12-month, randomized, parallel-group, placebo-controlled trial using established cognitive, global, or functional measures as primary outcomes provides a path to drug approval, as long as the drug actually works. However, even this setup is potentially problematic because a 12-month placebo-controlled trial may be considered unethical, given that there are now drugs available to manage AD and because the disease is known to be progressive (Kawas et al., 1999; Karlawish and Whitehouse, 1998).

In an effort to manage AD early and to move from symptomatic to disease progression trials, the field has begun to design and initiate studies in people with MCI. The MCI patients selected for these trials are presumed to have prodromal AD and are likely to progress to an AD diagnosis within several years. A common trial design is to determine if treatment of MCI patients for several years can slow clinical progression and delay time to AD. However, there are no established guidelines for MCI trials, and it is clear that a purely symptomatic treatment effect may delay time to AD diagnosis. To help substantiate potential effects on disease progression, potential treatment effects on biologic indices of disease severity, such as magnetic resonance imaging (MRI) of hippocampal atrophy, can be examined.

One area that has yet to be adequately addressed is the design of and outcome measures in primary prevention trials (Leber, 1997). It is now accepted that AD pathology in the brain begins many years before clinical symptoms emerge and that delaying onset of symptoms by 5 years would have a major impact on disease prevalence (Brookmeyer et al., 1986). A major barrier to conducting such trials is the enormous effort and cost of conducting periodic clinical evaluations to determine if subjects have declined or developed dementia.

Enrichment strategies can be used to select subjects for prevention trials who are at increased risk of developing AD (e.g., high age, family history of AD, apoE-4 genotype). Enrichment may facilitate “proof-of-concept” prevention trials by enabling designs with smaller sample sizes and shorter observation periods but with the potential tradeoff of reduced ability to generalize the results. A more ideal selection strategy will use biologic markers of early AD brain pathology, when such markers become available.

**Recommendations**

Phase I and II trials could be expedited by use of a sequential cohort design to quickly identify the maximum tolerated dose (MTD) and provide some evidence of efficacy. Ideally, one would be able to use clinical and nonclinical markers that are predictive of the efficacy of drugs for AD, e.g., functional magnetic resonance imaging (FMRI) and positron emission computed tomography (PET) brain imaging techniques that evaluate hippocampal atrophy, glucose uptake, radiolabeled β-amyloid probes, or cerebral blood flow (Tanaka et al., 2001; Grady et al., 2001). Clinical programs could be speeded by conducting three 6-month placebo-controlled studies and three long-term safety studies.

With regard to primary prevention trials, there is a great need for new or improved assessments, with increased sensitivity and efficiency that can be used to assess patient status. Costs could be greatly reduced by minimizing the time requirements for clinical staff, data monitoring, and data entry. An important research goal should be the development and evaluation of new instruments in relevant domains that are sensitive, reliable, and valid for detecting change in normal aging and early AD, that can be self-administered and do not require significant involvement of professional staff, and that minimize requirements for data monitoring and data entry. New uses of technology, such as computerized assessments and telephonic methods, are needed in this field.
LACK OF SURROGATE MARKERS

The lack of robust, surrogate markers for therapeutic endpoints remains a serious barrier in the clinical development of drugs to manage AD. The availability of such surrogates would result in a rapid acceleration of AD drug development. For example, there are an increasing number of compounds available for multiple sclerosis following the acceptance of MRI plaque quantitation as a measure of drug efficacy.

Recommendations

Any robust predictor of clinical outcome would result in a rapid acceleration of AD drug clinical development. There has been some progress in this area, but more is needed. Putative markers in cerebrospinal fluid (CSF) or blood such as β-amyloid and tau are not adequately validated and may not be sensitive to longitudinal progression and treatment effects. Neuroimaging markers, such as hippocampal atrophy as determined by MRI, are well validated and reasonably sensitive for use in long-term trials but are not suitable for short-duration, proof-of-concept trials. Neurochemical brain imaging methods such as PET have potential but require validation. More research is needed to develop and validate these and other markers. DNA microarray technologies and emerging proteomic technologies may be useful to screen for surrogate markers. There is also a need to develop an infrastructure to speed up validation studies, such as large-scale biologic sample collection from ongoing studies of aging populations.

BARRIERS IN ACADEMIA

Academic drug discovery and development programs are typically underfunded and lack infrastructure, in terms of staff and equipment, especially at the preclinical level. In addition, there is a general lack of interaction and collaboration between necessary teams of researchers. The environment and structure of academia often limit projects because of the multidisciplinary nature of drug discovery research and the still largely classic disciplinary organization of academia. For example, pharmacology and medicinal chemistry programs are frequently not integral components of medical schools. Increasingly in science and medicine, the important questions are those concerned with problems, rather than disciplines; solving problems typically demands interdisciplinary approaches. As in industry, successful academic drug discovery and development requires extensive collaboration among biologists, chemists, and clinicians.

There is also a lack of alternative career opportunities in academia for scientists outside the classic tenure-track path. Highly skilled scientists are needed to operate core facilities for drug discovery and drug development. Because they lack viable career paths to pursue drug discovery, academia does not attract those with the necessary skills, and there is high turnover of the best persons, who often leave for the pharmaceutical or biotechnology industries. Most training in pharmaceuticals and medicinal chemistry occurs in industry, not in academia.

Another major barrier to drug discovery and development in academia is that National Institutes of Health (NIH) review panels typically lack expertise and mission in drug discovery and development and turn down many such programs. The panels simply do not fully appreciate the interdisciplinary, cross-disease research emphasis that is central to drug discovery research. Removing this barrier will depend on organizing review groups with members having appropriate scientific, technical, and institutional backgrounds. Experience and familiarity with drug discovery and development in academia should be criteria for the selection of reviewers for applications regarding AD drug discovery and development research, even if the reviewer’s disease focus is not AD.

In addition, the NIH itself must decide whether drug discovery and drug development (at least certain aspects of it) are part of its mission. We believe this approach to drug discovery and development is now changing (e.g., http://grants.nih.gov/grants/guide/pa-files/PAS-99–034.html), as interest in translational research grows at the NIH and academic institutions (Gelijns et al., 1998). Royalty payments have become an alternate source of revenue for academic institutions; some universities receive tens of millions of dollars per year in royalties and other payments from the commercialization of their intellectual property (Lehrman, 1993). Combined with newer technologies that are affordable to academics, such as robotic combinatorial chemistry and “gene chips,” the opportunities for drug discovery in academia have never been greater.

Recommendations

Although many of the issues related to barriers to drug discovery in academia are generic problems in academia, we believe that the approach to facilitating drug discovery and development should be disease specific. Although infrastructure and expensive equipment such as nuclear magnetic resonance (NMR) machines may be needed, equipment and buildings alone will not get the job done. For example, with AD, neurobiologists and other neuroscientists need to be joined with medicinal chemists and pharmaceutical chemists to create a team that can have an impact that is project oriented, affordable, and potentially fundable by granting agencies. Most
academic scientists lack the expertise to carry out all the necessary steps in preclinical drug development research. A “how-to” manual, showing the necessary steps and highlighting pitfalls in the process, combined with a directory of resources, would be useful. New funding models should also be explored to provide support for core facilities and highly qualified non-tenured staff in academic institutions, such as creation of endowments for core facilities and pharmaceutical and biotech consortia.

### BARRIERS IN BIOTECHNOLOGY

Alzheimer disease drug discovery and drug development are generally considered high risk. For small biotechnology companies, where much innovation occurs, attracting capital for early-stage, high-risk projects is difficult, especially that related to chronic disease when the return on investment is seen as distant. The cost of conducting clinical trials especially is a major barrier to small companies; risks are high, and the probabilities of scientific success are low. As a result, external sources of funding are important; key sources include the NIH Small Business Innovative Research (SBIR) and Small Business Technology Transfer Awards, Cooperative Research and Development Agreement (CRADA) awards, and venture philanthropic funding.

### Recommendations

Philanthropic organizations and government can play important roles in helping small and mid-sized biotechnology companies with early-stage, high-risk AD programs. The Institute for the Study of Aging supports AD drug discovery and development efforts and has recently announced a Request for Proposals (RFP) program for drug discovery in AD for the biotechnology industry. Other philanthropic organizations need to join this effort. Government programs, such as SBIR and CRADA, can be improved so they play a bigger role in the process.

### BARRIERS IN THE PHARMACEUTICAL INDUSTRY

Barriers to AD drug discovery and drug development at the major pharmaceutical companies include lack of flexibility, concern about the business risks associated with developing drugs for AD, the perception that the AD market is not currently large enough to justify major research and development investment, and that limited resources can be more effectively used in developing new formulations and combinations of existing drugs. However, the size of the market is a perceived barrier, not a real one. As outlined previously, the size of the market for a safe and efficacious drug is potentially the 8–10 million AD sufferers in the seven major pharmaceutical markets, a number that is increasing rapidly. That sales of the currently available drugs are relatively low is a reflection on the efficacy of those drugs and the poor recognition and diagnosis of the disease, not on the potential market.

### REGULATORY BARRIERS

Another issue that affects the pharmaceutical and biotechnology industries is the lack of international harmonization of clinical trial and regulatory requirements (Spiegel and Irwin, 1996). For example, the US Food and Drug Administration (FDA) requires two pivotal studies to demonstrate the efficacy of a drug; the European Committee for Proprietary Medicinal Products requests two studies; and Japanese authorities requires one study. The duration of the study treatment period required also varies, from 3 to 12 months, depending on the nation. The requirements for demonstrating long-term safety also vary, as do efficacy measures. Designing all these requirements into a clinical program increases time and costs; harmonization would reduce both.

A significant barrier to AD drug development is the definition of therapeutic benefit for AD drugs. The FDA requires that a drug 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); a variety of global clinical assessment tools are used. Although other symptoms of AD (e.g., activities of daily living impairment or behavioral symptoms) have been studied as secondary efficacy measures, the FDA has not formally accepted these symptoms as acceptable primary outcome measures. In particular, adverse behaviors are considered nonspecific outcomes, although they represent some of the most difficult aspects of disease management. This restrictive definition of the disease is biased toward drugs that enhance performance.
on memory-based tests. The development path for cholinergic replacement drugs is, therefore, relatively straightforward. However, drugs designed to slow disease progression have a more complex path toward registration and approval.

**Recommendations**

A less restrictive definition of the disease that is not biased toward drugs that enhance performance on memory-based tests would be helpful. International regulatory harmonization would reduce costs and trial design complexity.

**SUMMARY**

Much progress has been made in AD drug discovery and development, but many challenges and barriers remain. There is still a lack of validated therapeutic targets, compounded by the clinicopathologic heterogeneity of the disease, both in terms of multiple pathways of pathogenesis and risk factors in patients. More fundamental research is sorely needed. Better animal models of AD are needed that more adequately represent the many features of the disease. There are also issues of availability and access to existing animal models for use in exploring therapeutic targets and drug screening. In academia, there are barriers to translational research in AD. Underfunding is an important problem, especially for programs to promote and develop collaboration between multidisciplinary teams. As an example, there is a great need to promote collaborations between medicinal chemists who can develop compounds for new targets identified by neurobiologists. The NIH and AD-specific foundations should recognize that translational research for AD is now an achievable goal in academia and a worthy part of their funding missions; both should increase the allocation of funding for such programs and establish review committees with expertise in drug discovery and development. There are also barriers affecting the biotech and pharmaceutical industries. AD drug discovery and development is high risk. There is also a failure to appreciate the potential market opportunities. There is a great need for increased investment in AD programs, despite their high risk; the huge potential rewards for an effective drug should provide incentive enough. These barriers are surmountable, and we are at a point where great advances in AD therapeutic agents should be possible. Merely delaying the onset of the disease by 5 years would reduce the incidence by 50% and would save billions of dollars (Brookmeyer et al., 1998); this should be an achievable goal.

**REFERENCES**


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