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Commentary on “A roadmap for the prevention of dementia II. Leon Thal Symposium 2008.” Facilitating Alzheimer’s Disease Drug Development in the US

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Alzheimer’s disease (AD) therapeutic research is on the brink of major advance; the field is poised to add effective disease-modifying treatments to our current symptomatic agents. The basic scientific understanding of AD pathophysiology has yielded a number of exceedingly promising targets for intervention, with many drugs now in various phases of clinical testing. Whether we reach a breakthrough within five years or in fifteen years will be determined by the national will.

In addition to financial support (specifically NIH funding for AD translational research), there are several concrete steps that will facilitate progress on bringing the next generation of therapeutics to the market. These steps are related to some important issues specific to the development of disease-modifying AD treatments, as well as some broader clinical research issues.

1. Change the diagnostic criteria for Alzheimer’s disease

A diagnosis of AD should indicate the presence of the neurobiological abnormalities that, if unchecked, will eventually lead to dementia. At present, diagnostic criteria require the presence of dementia¹. But we now have tools that allow the documentation of reduction in cerebral metabolic rate², amyloid and tau dysregulation³, amyloid deposition in brain⁴ and regional brain atrophy⁵ many years before the appearance of the functional impairments of dementia. Further, we can measure subtle cognitive decline many years prior to clinically important impairment⁶. Based on observations regarding the prevalence of brain amyloid deposition and mild cognitive decline in the non-demented elderly, we can estimate that the number of cases of “neurobiological AD” is at least two to three times larger than the number of cases of clinical AD according to current criteria. That is, there are now at least 10–15 million people in the US with AD pathology, though only about 5 million are demented. Appreciation of the “true” prevalence of AD will encourage more reasonable allocation of resources. But more important, it is the millions of people with early AD neurobiology that represent the proper target population for effective disease-modifying interventions. The research-criteria for AD recently proposed serve as an excellent start to the process of adjusting diagnosis based on our growing understanding of the neurobiology of AD⁷.

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2. Develop a feasible regulatory pathway for disease-modifying treatments

Disease-modifying treatments target AD neurobiology rather than clinical symptoms, and for significant efficacy in altering the clinical trajectory such treatments should be initiated years prior to dementia onset. If drug studies are limited to dementia patients, they may be doomed to failure (or very limited success).

We must facilitate the testing of drugs in the pre-dementia stage, perhaps in the asymptomatic stage. This means that we must adjust current criteria for drug approval. At present, an AD drug must be shown to favorably influence cognition and global clinical or functional status. Early in the neurobiology, when symptoms are minimal or absent and function is normal, it cannot be possible to favorably influence cognition and functional status in a workable period of time. Therefore, the definition of the disease must be moved back to encompass early stages of diagnosis, and a regulatory pathway including surrogate markers of the neurobiology must be developed. A realistic approach to validation of AD surrogates must be adopted by the field and the FDA.

3. Facilitate pre-competitive collaboration on drug development methodology

The necessary methodology will require large efforts to develop usable biochemical and imaging biomarkers of AD neurobiology, link those biomarkers to cognitive, behavioral and functional aspects of the disease, and establish appropriate analytical tools to demonstrate drug efficacy. No single company, institution or even sector can readily accomplish this. Pre-competitive collaboration has been established in efforts such as the Alzheimer's Disease Neuroimaging Initiative⁸ (which has been funded jointly by NIH the pharmaceutical industry, and includes industry, academic and regulatory collaborators). This type of collaboration must be expanded and intensified to yield workable solutions to today's trial design conundrums in the near future.

4. Galvanize the nation to support and participate in clinical studies

The number of AD subjects and families required to enroll in current trials is many fold higher than just a couple of years ago; the Elan/Wyeth bapineuzumab program alone requires 4000 subjects. This increase in subjects needed reflects not only the growing number of promising treatment strategies (active and passive immunotherapy, gamma secretase inhibition/modulation, beta secretase inhibition, anti-aggregation agents, mitochondrial stabilizers, neuroprotectants), which is very good news, but also the huge trial size and length required for disease-modification drug development.

We must not allow unmet trial recruitment needs to create a bottle-neck in AD drug development. To avoid this, a national drive to broaden awareness of the need for widespread clinical research participation, as well as the altruistic rewards of such activity. The health care professions, government (White House, Surgeon General, Congress), the entertainment world and media resources must all be brought to bear.

A national registry of subjects and families affected by (or at risk for) AD should be one component of this effort. This would serve multiple purposes, including facilitation of communication regarding the disease, its current treatment and research developments, as well as information regarding clinical trial opportunities. It is possible to establish such a system with appropriate attention to privacy concerns. It may be feasible to make use of the growing commitment to electronic medical record systems (which might facilitate the invitation to

individuals to join a registry, and if consent is provided, the automated transfer of relevant information into the registry).

5. Provide better support to clinical trial sites

Greater participation in trials also requires a stronger AD trial infrastructure. The number of qualified trial sites in the U.S. (and internationally) is insufficient for current needs. Out of necessity, the largest drug studies are being conducted at academic, commercial and private practice sites lacking in appropriate trial methodology training and resources. The result will likely be an increase in subject heterogeneity, measurement variance, and drop-out rates; this will drastically increase the chance that an effective drug will fail in clinical trials. To strengthen our clinical performance sites, we must improve training and retention of investigators, provide infrastructure support to sites, increase site reimbursement rates for subject enrollment, and strengthen and expand national trial organizations such as the Alzheimer's Disease Cooperative Study⁹.

6. Reduce unnecessary local regulatory barriers

AD clinical trials currently in progress range in size from 1 to 270 sites. For large multicenter trials, an enormous effort is required to obtain local Institutional Review Board (IRB) approval at each participating site. While commercial and private practice sites may have the option of utilizing private central IRBs, academic sites must obtain individual review and approval at each institution. This means that a trial protocol and consent form is independently reviewed, in exhaustive detail, by dozens of committees. The time, effort and expense of these redundant reviews (and the endless "wordsmithing" of consent forms), which have to be repeated with each trial amendment, is enormous and discouraging. A single, national IRB, with appropriate expert representation, would provide more meaningful oversight at a small fraction of the effort.

7. Assure that companies that make the huge investments in AD drug development can expect reasonable profits

The risks and costs of investing in AD therapeutics can deter large and small companies. The potential payoff in societal gains is of course enormous, but we must assure that corporate investment is adequately rewarded. Since the development timeline in this field is so long, adjustment to the protections of intellectual property value are necessary. For example, an extension of the period of market exclusivity for first-in-class AD drugs may be required.

None of these seven items requires a huge financial investment; they can all be readily accomplished with an appropriate national commitment to the development of effective prevention and treatment for AD. No U.S. health care investment will have a greater payoff.

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