Meeting Report

A roadmap for the prevention of dementia: The inaugural Leon Thal Symposium

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1. Background

In February 2007 our field suffered the tragic loss of Dr Leon Thal, a towering figure in both the Alzheimer's disease (AD) research and clinical communities. Leon's life and impressive career were honored at a symposium convened by the Lou Ruvo Brain Institute (LRBI) on December 3rd and 4th, 2007 in Las Vegas, Nevada. In an attempt to focus our energies on the concerns and interests that Thal advanced in both his research and clinical practice, the symposium brought together a group of clinicians and scientists, most of whom had worked with or trained under Thal, to focus attention on treatments that might prevent AD.

Leon Thal was an early pioneer in the search for AD symptomatic therapies, but at the time of his death in 2007, he had shifted his focus to prevention. Among his many scientific endeavors, Thal was a scientific advisor to the LRBI, a 501 c(3) not-for-profit corporation based in Nevada, created to promote collaborative research on neurodegenerative disorders that affect memory, movement, or mood, including Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis (ALS).

The Institute was established in memory of Lou Ruvo, who died of AD in 1994 and had been Thal's patient. It was therefore fitting that the Institute convene the Leon Thal Symposium on the Prevention of Dementia not only to celebrate Leon's extensive contributions to therapeutic research but also to project his dream for the future. The participants of this "think tank" style meeting included international experts in dementia research and loyal friends and colleagues of Thal. The deliberations at the meeting focused on the daunting challenges of formulating new national and international strategies for accelerating the process of drug discovery, development, and clinical trials. The ultimate aim was to start the process of crafting a roadmap for public policies that would radically change current paradigms of research into effective therapy development for the prevention of dementia.

The convener of the symposium, Dr Zaven Khachaturian, charged the assembled scientists to think creatively and without boundaries, as Thal would have done, in crafting recommendations for what could turn out to be a paradigm shift in drug development. The specific charge of the participants, organized into four "work groups," was to prepare draft recommendations for changing policies concerning the following issues and challenges:

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- What are the major challenges or barriers to progress in developing new treatments for prevention?
  - For very early disease (ie, mild cognitive impairment [MCI]).
  - For mild to moderate disease.
  - Inappropriate requirements by regulatory agencies for demonstration of prevention or disease modification.
- What are the best strategies to overcome such impediments, and are there special opportunities that could be exploited?
  - Promising biomarkers of disease progression.
  - Promising biomarkers for use in early detection studies.
- Do we have the right therapeutic targets?
- Are current study designs and analytical methods for clinical trials adequate or appropriate for prevention trials?
  - Likely causes and impact of changes in the trajectories of placebo-responding subjects in clinical trials during the past 5 to 10 years.
  - Incentives to establish "captive populations" with naturalistic, longitudinal follow-up for enrollment in future disease progression studies.
  - Novel study designs, such as Bayesian approaches to dynamic enrollment and dose titration.
- Are there any changes in public laws governing drug development and/or patents that would accelerate the process?
  - Patent extensions for preventive therapies aimed at decreasing looming public healthcare economic burden.
- Are there any different or new business models for financing the costs of therapy development?
  - A "MATRICS style" level of support from the National Institutes of Health to provide funding support for early phase development of promising therapeutics, with protection of intellectual property for later phase development by biotechnology or pharmaceutical corporations. (MATRICS [Measurement and Treatment Research to Improve Cognition in Schizophrenia] is a battery of cognitive tests developed originally for aiding in drug development for schizophrenia.)
- What are some of the strategies in managing the growing aversion to "potential risks" in scientific decisions and study designs, medical, financial, social, etc.?

This report is intended as a summary of the recommendations proposed by the participants of the first annual Leon Thal Symposium on Prevention of Dementia.

2. Introduction

AD research has exploded during the last 20 years, resulting in the identification of numerous possible pathogenic pathways and targets for intervention. Accompanying this mechanistic research, neuropathologic and imaging studies have revealed that the pathogenic process begins long before the first symptoms appear and that modifying the disease process, in contrast to treating symptoms, might likewise require intervention long before the disease becomes evident. The drug development and regulatory processes, however, have for the most part remained focused on treating symptoms rather than preventing disease or intervening in its progression. The traditional phase I, II, and III trials follow a common pathway, evaluating first safety and tolerability, followed by dose finding and early effectiveness, and culminating in efficacy trials designed to demonstrate that a drug is safe and has a beneficial clinical effect. This model, however, is not appropriate for evaluating preventive or disease-modifying treatments, where the clinical benefits might be so subtle and far into the future as to be unmeasurable within a reasonable period of time.

Multiple, interrelated barriers to drug development

The barriers to developing preventive therapies span scientific, structural, business, and economic issues. Although it is clear that the disease process that eventually results in neurodegeneration and dementia in AD begins early, the exact nature and timing of these early steps are not known. AD might even represent the culmination of a neurodevelopmental process that begins at birth; or it might be a reflection of the normal aging process that is accelerated in some people for unknown reasons. The absence of a complete animal model of the disease (as opposed to partial models of selective pathologies) has certainly dampened the discovery process. A better understanding of disease progression in the earliest stages should also lead to the identification of novel therapeutic targets for preventing disease. The answers to these questions will emerge only through increased efforts to understand the basic biology of AD and neurodegeneration, including greater reliability in identifying early/prodromal AD, cognitive measures that are sensitive to change in mild disease, and the effect of changing lifestyles, medications, and lifestyle adaptations as management of mild dementia undergoes further development. This will require support for very long-term longitudinal studies, yet inadequate funding for basic science has stymied progress in this fundamental area. In fact, although the burden to society from AD has increased steadily since 1990, funding for AD research has remained flat. Clearly, new funding streams need to be established to ensure progress in both basic and applied research.

As the drug development process moves from the basic science laboratories into clinical trials, infrastructural and regulatory barriers, along with different economic considerations, become paramount. Key players at this stage of the process include pharmaceutical companies, the Food and

Drug Administration (FDA), and clinical trial sites. Although drug development in general is risky, expensive, and time-consuming, developing preventive treatments increases the challenges many fold. As a result, demonstrating effectiveness in preventing a disease might require such lengthy trials that the patent life on a drug will be exceeded. Moreover, at this time, methods for designing and implementing prevention trials, including how to identify at-risk subjects and how to assess outcome for those trials, have not been fully established.

Responding to these multiple challenges will require flexibility and cooperation on the part of all stakeholders: clinicians, researchers, regulatory agencies, federal and private funders, Congress, pharmaceutical companies, and the public. A comprehensive strategic response to this challenge will require consideration of how to manage the risks that each of these stakeholders face. But the risk of not developing such a strategy is far greater in terms of the public health and economic impact.

Identifying and surmounting scientific barriers

The search for drugs to prevent or treat AD has largely been predicated on biochemical targets selected because of their relationship to known abnormalities in AD brains, eg, accumulation of amyloid-beta peptides and acetylcholine deficiency; or because they were thought to cause the neuronal death that typifies the disease, eg, excitotoxicity and oxidative stress. Additional targets that need to be explored, particularly for the prodromal stages of AD, include the loss of synapses in affected brain regions (from a deficiency in the production of new synapses or accelerated turnover of existing synapses, or both) and disrupted synaptic function.

Synapses include, in addition to presynaptic elements (the terminal boutons that synthesize neurotransmitters and then store and release them, largely from vesicles), highly specialized postsynaptic membranes, eg, the dendritic spines of excitatory (primarily glutamatergic) neurons. These spines contain postsynaptic densities with large numbers of characteristic proteins, including, for example, neurotransmitter receptors. Formation of new brain synapses is initiated by the outgrowth of neurites from presynaptic membranes; this structure comes into apposition with a dendrite and induces formation of the dendritic spine. Any pathologic process leading to synaptic dysfunction would be expected to negatively impact on cognitive function, and alterations in the growth, maintenance, or plasticity of synapses in the cortex might very well be responsible for clinical manifestations of the disease. There are a variety of intriguing therapeutic targets at this cell level that could be targeted for discovery. For example, a number of compounds reportedly can increase dendritic spine levels in experimental systems; however, only a few of these have been tested in pilot trials with AD patients. Such compounds or others that stimulate neu-

rite outgrowth or synaptic plasticity or slow the turnover of synapses could theoretically slow the course of AD.

Amyloid and tau have also not been fully exploited with respect to their roles as AD targets, and *APOE ε*4, the single most important genetic risk factor and a potent modulator of synaptic integrity and plasticity, might also be a target. Other targets that should be explored for their relevance to AD, particularly early stage AD, include those related to cerebrovascular disease, plasticity, and neurogenesis. Investigations of these and other targets could lead to more clarity in the question of how AD differs from normal aging and how and when intervention should or could begin.

To date, therapeutic efficacy has only been demonstrable with symptomatic therapies during relatively limited time spans. Demonstrating efficacy remains a major hurdle that has yet to be surmounted with approaches targeting disease pathogenesis, at least in part because of the absence of validated biochemical or imaging biomarkers. This leaves only a reliance on surrogate markers, including but not limited to cognitive readouts that are highly variable and disease-stage responsive. Thus, a second major scientific barrier is the development of validated biomarkers of AD that provide an informative readout of the targeted therapeutic effect. For example, it is not clear how targeting *APOE ε*4, synaptic markers, or neuritic abnormalities could be confirmed in an individual patient. Broadly defined, a biomarker can be any sort of marker that indicates a biologic state. This includes measurement of substances in plasma or cerebrospinal fluid (CSF); neuroimaging with magnetic resonance imaging (MRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT); gene expression profiling, electrophysiology (including event-related potentials), and even results of cognitive/neuropsychological tests such as tests of executive function or subtle memory changes. Moreover, a validated biomarker for use in early detection (with high sensitivity and specificity) and/or for tracking early disease progression (with high sensitivity being most important) might result from the synergistic, multimodal use of more than one of these technologies listed above. Biomarkers for AD serve a number of different roles: quantifying an individual's risk of developing AD; recognizing the underlying pathology of AD regardless of its clinical relevance, recognizing the presence of a clinically symptomatic disease state, tracking progression of the disease along the clinical spectrum (which will be important for secondary prevention), and reflecting the action of drugs or non-drug interventions. Surrogate markers can be any set of biomarkers or cognitive measurements that change with a treatment effect, regardless of the specific therapeutic target. It should be obvious that this exercise of biomarker and surrogate marker identification and validation will require an iterative process that must be conducted concurrently with therapeutic intervention trials.

More sensitive biomarkers are needed for each of these

roles, and in evaluating each biomarker technology it will be important to appreciate the different roles it might fulfill. Thus, for each biomarker more naturalistic, longitudinal data are needed on whether it is predictive, whether it adds anything to the diagnosis, whether it provides information about the stage of disease, whether it can be used to determine whether an individual should be included in a clinical trial, and whether it "moves" with a therapeutic intervention and thereby indicates efficacy. The process for identifying biomarkers will be aided by a clear understanding of the different purposes that different types of biomarkers would serve.

The Alzheimer's Disease Neuroimaging Initiative (ADNI), among a few other large-scale efforts in progress, has begun to make inroads in this area by enrolling people who are cognitively normal or who have MCI and following them during a 3-year period to the point where they develop MCI or become demented. Subjects are stratified on a number of parameters, such as presence of the *APOE ε4* allele and sex, and then followed with a variety of assessments (neuroimaging, biochemical markers in CSF and other fluids, and cognitive/neuropsychological tests). Data from other trials, such as the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) and Gingko in Evaluation of Memory (GEM) studies and several other prevention trials, could be combined with ADNI data to provide a broader perspective. Ultimately, however, longer prospective studies will be required, and this will require a commitment from the National Institutes of Health (NIH) to fund longer longitudinal studies.

These studies might also reveal that it is not a single biomarker but the relationships among a number of biomarkers that can provide evidence of risk, prognosis, state of disease, or response to treatment. Moreover, these sets of biomarkers might respond in combination differently among distinct patient populations/stratifications. Such an outcome is particularly likely for a disease like AD because there are multiple pathologic events that are occurring simultaneously, together leading to the clinical disease. Thus, the study of patterns of biomarkers will require new analytical methods that take a "systems" approach to understanding the disease.

Meanwhile, a number of new technologies are in development, including new SPECT ligands and new techniques with spectrophotometry. Again, thinking "outside the box" is needed. For example, the National Institute of General Medical Sciences (NIGMS) has requested applications for molecular probes using nanotechnologies to identify molecular lesions at a single cell level; and new technologies in medicinal chemistry might lead to the development of new ligands that can be used to visualize, in a living individual, steps in the cascade of events that lead to AD. In developing these new technologies, it will be important to keep in perspective whether they move the science closer to understanding why cognitive deterioration occurs in AD. At the same time, however, new methods might lead to a wealth of new hypotheses, so one would not want to dismiss a new technology a priori simply for lack of a hypothesis to test.

A final important consideration in the development of biomarkers is cost. Cheap, noninvasive biomarkers for early diagnosis at the point of care, ie, accessible by primary physicians, are sorely needed to stratify subjects according to risk, both for clinical management of those individuals and for enrolling them in clinical trials.

Identifying and surmounting infrastructural barriers

The infrastructure that supports development and clinical trials of treatments for AD crosses research, clinical, business, and regulatory domains, each of which introduces a number of barriers to progress.

At the basic and translational research levels, the peer review system at NIH reinforces scientific orthodoxy and leaves little room for out-of-the-box thinking. Submitted grants in well-traveled areas, such as study of the role of toxic forms of the amyloid beta protein, tend to be better documented and thus have a higher likelihood of getting funded. Although the NIH has made some attempts to respond to this problem by introducing the criteria of novelty into the R01 reviewing rubric, projects with novel ideas or that challenge existing ideas still have a higher hurdle to overcome if they are to get funding, particularly with the current low funding levels. Participants at the symposium agreed that a structural change is needed at NIH that would result in channeling more research support to speculative projects, and that researchers should be afforded greater flexibility in using their funding for exploratory research.

As drugs move through the pipeline from research to development, not only are more agents needed (including combinations of drugs), but new models are also needed for conducting clinical trials efficiently and productively. The current system in which trials are conducted through commercial sites and academic AD centers (ADCs) has not been able to keep up with the increasing numbers of subjects required for research studies. Problems include insufficient support for clinical research sites, inadequate infrastructure at the most capable institutions, and fragmentation of the clinical care of research volunteers. Because academic institutions tend to have higher overhead rates and more local regulations, they cannot compete with commercial drug development sites, and their contributions are likely to gradually become even more limited over time. More emphasis is needed on establishing clinical trial sites that work efficiently in an integrated network to collect data including biomarker data for registries; collect, bank, and share biologic materials; and acquire and maintain research subjects and follow large cohorts of subjects longitudinally, including maintaining their enrollment during "slow periods" between federally funded or industry-sponsored

clinical trials. Improved data collection might also require development of new Web- or telephone-based technologies to interview subjects and evaluate cognitive function. One suggestion to address these problems is to establish a large nonprofit clinical research organization (CRO) arm of the Alzheimer's Disease Cooperative Study (ADCS), which would be managed as a separate unit of the ADCS. This nonprofit CRO would be responsible for harnessing the talent and expertise at ADCS member sites and would work in partnership with industry sponsors and other organizations to maintain an efficient national network for clinical research in AD.

A second issue relates to the sharp distinction between clinical care and clinical research. Understandably, research grants cannot pay for clinical care, and clinical payers are hesitant to pay for research. Most established AD research centers have dropped clinical care from their mission to focus on research. From the patient's perspective, this means that they must go to different places for expertise in clinical care and for expertise in research opportunities. If clinical care and clinical research were routinely accomplished in the same setting, it would aid the recruitment and retention of patients in clinical trials. Clearly the low Medicare and other third-party reimbursement for clinical care of AD patients is a factor that "disincentivizes" the most expert centers from keeping patient care at the heart of their activities.

Trials will also have to extend their scope internationally, and there already exists a program within the NIH for developing an international network to recruit and evaluate people with early-onset, dominantly inherited AD. Standards will have to be developed across nations, languages, and cultures for evaluating and following individuals in a consistent, reproducible manner. This is particularly challenging because of the effects of language and culture on certain psychometric measures and quality-of-life indicators. Finally, federal agencies need to reexamine their reluctance to partner with pharmaceutical companies, perhaps through Cooperative Research and Development Agreements (CRADAs), which facilitate partnerships between federal agencies and non-federal collaborators. Again, the ADNI consortium project is a terrific example of one successful large-scale effort along these lines.

New trial methodologies are also needed. In particular, more emphasis needs to be focused on phase II studies, especially studies that include biomarkers to ascertain diagnosis as accurately as possible and as measures of surrogate effects. Some companies have moved on to phase III studies without adequate phase II data, and this has resulted in some perceived failures among drugs that might have otherwise demonstrated some degree of efficacy if dosed appropriately. Suggestions were made to require phase IIa studies, which would focus on safety, dose finding, and understanding the mechanism of action before moving to phase IIb studies, which would be proof-of-concept trials at particular doses. However, the time required for adequate phase II studies disincentivizes pharmaceutical companies from drug development, especially for disease-modifying indications that require large, lengthy phase II trials. This issue is not likely to improve until there are changes in the FDA drug approval process as discussed below. It might also be necessary to reconsider the requirements for establishing proof of concept for a drug or a class of drugs intended to prevent disease. For example, in a prevention trial, a change in neuroimaging or another biomarker might be an appropriate primary outcome measure.

Pooling placebo data is another strategy that might be useful for increasing the efficiency of trials, particularly because some recent studies suggest that placebo groups appear to be declining more slowly than in earlier studies. Possible reasons for this might include a relaxation of inclusion criteria (particularly for disease modification trials), resulting in enrollment of earlier stage patients and a greater proportion of slow decliners, improved management of dementia patients, and improved lifestyle adaptation skills. Another possibility is that these groups are taking other medications that affect symptoms and/or progression. For example, nearly all trials are now add-on therapies over cholinesterase inhibitors and N-methyl-D-aspartate antagonists, which impact on progression rate and variability in the "placebo" arm. Thus, it is critical to take a new look at the natural progression of the disease in patients taking these medications during time intervals that are relevant to disease modification studies. It should be recognized, however, that pooling placebo data among trials conducted under dissimilar conditions in different patient cohorts will create complexities of analysis that will need to be handled carefully.

Clinical trials also might be more efficiently conducted in narrowly enriched high-risk population samples (eg, patients who carry at least one $APOE$ $\varepsilon4$ allele), possibly matched to the mechanism of action of the drug. Extending pharmacogenomics to other relevant markers (ie, BuChE, cyp46, etc) might be equally important. Enriching samples carries its own set of limitations, however. Although a quicker effect might be observable and thus shorten the trial, conversely there might be a slower effect and thus rejection of a drug that could be useful in another population. A potential problem associated with conducting trials in enriched population is that labeling might only cover that group of subjects. However, accepting this risk might be key to identifying therapeutic efficacy in such a heterogeneous patient population, requiring follow-up prospective studies when pharmacogenetic signals are identified.

Another possible strategy for testing compounds that might affect cognitive decline is to select subjects not because they have AD (and are therefore already significantly impaired), but because they have other conditions that also result in cognitive decline and/or other AD-associated pathologic changes such as amyloid deposition, for exam-

ple, subjects with neurosurgery-induced stroke or traumatic brain injury. However, this approach carries the alternative risk that the results might be only partially relevant to AD and thus could be misleading. Again, follow-on prospective studies in an AD cohort would be needed.

One of the most innovative approaches to restructuring clinical trials is the development of adaptive trial designs. Adaptive clinical trial designs that use Bayesian statistical models might potentially provide greater flexibility and efficiency as well as the ability to identify efficacy in smaller-sized clinical trials. Traditional models of clinical trial design require a priori power analyses to estimate needed sample sizes. The clinical trial protocol is then "locked in" to a specified designation of groups, dose levels, sample sizes, and duration until trial conclusion. The data are then unblinded, and the success or failure of the trial largely depends on achieving statistical significance at a 95% level of confidence. In the event that the P value on the primary outcome measure falls at, for example, $P = .1$, the trial is either designated a failure and the drug is abandoned, or the trial must begin again with a modification aimed at substantively increasing the likelihood of demonstrating efficacy.

In contrast, adaptive trial designs use interim sampling of data during the performance of the trial to gain real-time, "on-line" information regarding required sample size, trial duration, and dosing groups to more efficiently identify futility or efficacy of a drug. This approach provides a greater level of flexibility than traditional trial designs and hypothetically shortens the time and group size needed to identify a clear end point. Importantly, this design allows extension of a trial in the event that trends toward significance indicate that an expansion of the numbers of subjects or duration of monitoring is needed. The intermittent analysis of data from the ongoing trial requires a statistical cost that must be repaid in the size of the sampling pool, but the efficiency of the design is highly likely to streamline trials significantly. There should be greater study and understanding of such trial designs and implementation by the AD research community as indicated.

Many of these proposed changes in trial design will require concurrent changes in how the FDA applies approval rules to drugs in development, particularly for preventive treatments with more subtle and hard-to-measure benefits. One suggestion was that the FDA might consider conditionally approving drugs for preventive treatments under tightly regulated conditions even when those drugs achieve only minimal or moderate results in terms of efficacy. For example, approval might be given for a limited population group with the condition that postmarketing trials include biomarker studies. Conditional approval might be granted after one or two studies (including a well-designed phase II study), with final approval dependent on further replication of safety and efficacy results.

Another regulatory barrier to drug development is the institutional review board (IRB) as it currently exists. IRBs tend to slow the drug development process, particularly when trials are conducted across multiple institutions. One suggestion was that national or centralized IRBs be established for academic sites; however, this might require a change in laws because universities might not be able to legally cede their IRB authority to other institutions. Further investigation of this option, including expert legal opinions, will be needed.

Identifying and surmounting economic barriers

Because increased federal funding for biomedical research appears bleak at the present time, symposium participants suggested alternative sources. A clear statement from the Center for Medicare and Medicaid Services (CMS) regarding the eligibility of subjects recruited for longitudinal and other AD research studies for reimbursement from CMS would tremendously assist the current AD research effort. An additional option would be for Medicare and Medicaid to designate a small fraction of the cost of treating people with AD to support basic research. This option makes logical sense because the burden to the Medicare and Medicaid systems for treating AD will increase astronomically during the coming decades if the disease cannot be slowed. Another option is to redistribute NIH and Department of Defense (DOD) funds for cerebrovascular disease across multiple centers and institutes to encourage a more integrative examination of the relationship between cardiovascular disease and dementia. In addition, in response to numerous studies that have illuminated a link between brain injury and dementia, DOD should devote more resources to studies of neurodegeneration in later life among soldiers in the field who experienced head trauma.

Beyond the basic research arena, a major barrier to the development of preventive therapies involves current patent laws. Clinical trials for preventive treatments, especially for complex progressive conditions such as AD, are likely to require lengthy trials that exceed patent life on newly developed compounds. As a result, pharmaceutical companies will require incentives to pursue drug development in this area. Several suggestions were offered, although because this is an extremely complex area, a more complete analysis with expert opinion from patent lawyers will be needed before these suggestions can be operationalized. Suggestions included starting the clock on patent life only when proof of concept is established or granting a period of exclusivity (eg, 5 years) to companies that conduct prevention trials. Another possibility would be a governmental program that offers rebates to companies for the development of preventive drugs or nutraceuticals.

Incentives also must be devised to encourage companies to conduct more phase II research. For example, conditional approval might be granted on the basis of a single 1-year

phase III study if that study was predicated on a better, more informative phase II program that included dose finding along with biomarker studies. Conditional approval might also be offered after a phase II study that demonstrated the ability to change a biomarker, such as lowering amyloid beta, improving brain metabolic or electrophysiologic function, or improving cognition, with labeling only for the biomarker effect rather than for preventing or treating the disease itself. The lack of a validated biomarker makes this option more problematic, although regulators have been accepting some trials that use unvalidated surrogate markers with the provision that long-term data must continue to be collected on both the biomarker and its relationship to a clinical outcome such as emergence of the disease. Incentives such as additional exclusivity might also be offered to pharmaceutical companies that develop new biomarkers. This option would have the added advantage of bringing more players into the biomarker search.

Societal and cultural barriers

Another set of barriers to developing preventive treatments for AD involves the concept of risk aversion and crosses all the domains discussed earlier. Attention must be paid to identifying and managing these risks at all levels. As mentioned previously, the NIH grant review process is averse to ideas and concepts that stray from scientific orthodoxy because of the potential that public funds will be expended without a return. Systems must be established in the grant approval process that encourage innovation and the pursuit of novel ideas, recognizing and managing the risks of innovation.

In the industrial sector, the limited number of successful disease-modifying AD trials to this point has made some venture capitalists and pharmaceutical companies hesitant to engage in future AD drug development projects, judging that the risk of failure is too high. Changes in the design of clinical trials, the clinical trial infrastructure, and in the FDA's approval process (discussed earlier) might mitigate some of these concerns. Risks to patients who receive drugs in clinical trials and after approval also raise concerns among the public as well as at pharmaceutical companies, particularly in light of recent drug withdrawals and subsequent lawsuits. The AD community, in collaboration with pharmaceutical companies, needs to convince not only patients and the public but also investors that some level of risk is acceptable.

Risk aversion must also be addressed at the level of regulatory agencies, so that they will allow drugs for life-threatening, progressive, and complex diseases to move forward in the approval process despite a significant risk profile. Questions were raised among the symposium participants about some of the FDA's recent decisions to halt clinical trials. For example, some participants believed that the FDA "pulled the plug" too soon on the Elan trial of AN1792, an experimental immunotherapy meant to remove amyloid-beta from the

brain, whereas others believed that the trial was stopped appropriately, given that it was unclear how many more people might develop meningoencephalitis. Perhaps a process permitting a revised informed consent on the part of the patient and/or caregiver would be worth considering in this sort of situation. The conclusion of the symposium participants was that regulatory agencies need to take a less severe view of adversity to balance effectiveness with risk.

Overcoming any of these scientific, structural, economic, and social barriers will require commitment not only from the AD research community but also from the public as well. More money will be budgeted to NIH only when people demand it. Changes in patent laws will occur only when people demand better drugs. However, the limited success in developing AD treatments to date has created some ennui among the public at large. Symposium participants agreed on the need to work with other advocacy groups (including the Alzheimer's Association, which was represented at the symposium) to convince the public of the importance of these issues, so that they can create the noise that is needed to get the attention of Congress and the White House to move these ideas forward. Without a concerted effort to improve public awareness, these are issues that will cripple our efforts to accelerate progress.

Improved public education and awareness will also make a substantial difference in recruitment for clinical studies, according to a recent Alzheimer's Association study. One symposium participant noted that the percentage of her patients who agree to consider participating in a clinical trial has been decreasing in recent years, and at this point only about one third of her patients and/or caregivers are amenable to even discussing their suitability for clinical trials. The reason seems to relate to complacency, at least for the first few years of treatment with commercially available antidementia drugs, as well as to the general risk aversiveness and mistrust that currently characterize public discussions. Other clinicians have noticed a similar trend around the country, and there was general agreement among symposium participants that recruitment of subjects for clinical trials has become more difficult in recent years. This trend might be occurring for a number of reasons, such as decreasing trust in specialist providers or in the FDA to monitor patient safety in trials or lack of trust in the pharmaceutical companies that sponsor these trials, resulting from recent widely reported drug recalls for Vioxx (rofecoxib) and related pain relievers and for the increasing number of "boxed warnings" for widely prescribed drugs such as Avandia (rosiglitazone), a drug used to treat type 2 diabetes. Attacking this "universal crisis of trust" and the lack of knowledge among the public about AD, clinical trials, and drug development requires establishing a partnership with the media as well as fostering better relationships between academia and industry.

To some extent, the public's hesitancy to participate in clinical trials might reflect the perception that AD is not as serious, life-threatening, and ultimately fatal as other diseases such as cancer. More hard data and research are

needed to identify the reasons people decline to participate in clinical trials, because decreasing numbers of appropriate study subjects might be a serious impediment to efficient progress in discovering effective treatments.

Summary

The LRBI is committed to honoring the memory of Leon Thal and Dr Thal's goal of preventing AD. In addressing the complexity of developing preventive treatments for AD, participants at this symposium focused on formulating new strategies for accelerating the process of drug discovery, development, and clinical trials and on the need for collaboration among the NIH, FDA, academic medical centers, the pharmaceutical industry, philanthropic organizations, and the public to achieve this goal. The recommendations of the symposium represent a starting point for crafting a roadmap for public policies that will radically change current paradigms of research into development of effective therapies for the prevention of dementia.

Acknowledgment