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The Alzheimer's Disease Neuroimaging Initiative: Perspectives of the Industry Scientific Advisory Board

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Abstract The Industry Scientific Advisory Board (ISAB) consists of representatives from the private companies and nonprofit foundations participating as sponsors of Alzheimer's Disease Neuroimaging Initiative (ADNI). Currently 21 companies are represented including pharmaceutical, imaging, and biotech concerns, and two foundations including the Alzheimer's Association. ISAB members meet regularly by teleconference or face-to-face at ADNI meetings and participate in the ADNI Core groups, all administered and organized by the Foundation for the National Institutes of Health. ISAB 'deliverables' include dissemination of information to sponsors, assisting in scientific review of protocols and results, initiation and consideration of ''add-on'' studies and analyses, and generation of consensus positions on industry priorities and concerns. Although positioned as an advisory body, ISAB also actively contributes to the ADNI mission of identifying biomarkers of disease progression.

Keywords: ADNI; Alzheimer's disease; Consortium; MRI; PET; Biomarkers; Aβ

As noted in the introduction to this special issue, the turn of the century was a watershed time for Alzheimer's Disease Neuroimaging Initiative (ADNI). The request for proposal (RFP) for ADNI, capturing the goals of numerous academic, industry, government, and advocacy representatives and formed after years of debate, was issued by the NIA in early 2003. The final study protocol for ADNI, led principally by Michael Weiner, Leon Thal, and Ronald Petersen, was completed in March of 2003 and ADNI enrolled its first subjects in late 2004. Much has been accomplished over the past years for which we, as representatives for sponsor companies, are very grateful. At the same time, it is remarkable that so many companies have demonstrated willingness to contribute cooperatively to a project over this length of time. Such a commitment, with regard to both financial support and contribution of scientific expertise, challenges the needs of publicly held companies to show results, surpassed the turnover time for at least a few industry representatives to ADNI, and exceeded the lifespan of some of the founding members of this consortium. Those of us within pharmaceutical companies are reminded daily of the pressures facing our discovery and clinical research efforts. How did ADNI, as a complex industry/academic/government consortium succeed in the face of these difficulties, and will it succeed in the future?

The year 2000 marks a significant timepoint for the identification of possible treatments of Alzheimer's disease (AD) intended to interfere with disease progression. Fundamental work on the pathology of AD had occurred in the latter decades of the 20th century, notably the identification of abnormalities of processing of amyloid precursor protein in Down's syndrome and familial, early onset AD, and the key enzymes involved with amyloid protein catabolism

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[1,2]. This, in turn, led to the creation of transgenic mouse models over expressing beta amyloid (Aß) based on mutations found in the familial, early onset AD, providing an initial animal model for treatment discovery [3]. In a review published in early 2001, beta and gamma secretase inhibition or modulation, interference of Aß aggregation, and immunotherapy were all identified as candidate streams for discovery [1] and tool compounds appeared soon in the literature [4–7]. These still encompass most of the mechanisms being tested in clinic today.

Also around this time, there was growing consensus on the clinical signs and symptoms that might identify older subjects with mild cognitive impairment (MCI) at heightened risk for developing AD. These features, especially as outlined by Dr Ron Petersen at the Mayo Clinic [8], defined a cohort of patients at substantial risk for progression to AD (as defined by extant National Institute of Neurological and Communicative Disorders and Stroke / Disease and Related Disorders Association [NINCDS/ADRDA] criteria). These criteria were adopted as the basis for inclusion of subjects in clinical trials designed to test the effects of treatments on delaying disease progression. By 2001, sizable trials in MCI were supported by each of the sponsors who were marketing cholinesterase inhibitors at the time, in the hope of demonstrating an impact on disease progression. The uncertain status of MCI as a nosologic category led to early inclusion of anatomic magnetic resonance imaging (MRI) as a possible biomarker of disease or disease progression, although diagnosis of MCI relied exclusively on clinical assessment and performance on verbal memory tests. The thresholds and rigor with which MCI was defined varied across and sometimes during these studies, and MRI collection was not consistent; these measures were obtained at baseline only in the donepezil/Vitamin E trial and were obtained more comprehensively in the rivastigmine and galantamine trials [9–11]. To their chagrin, the sponsors of large studies on disease progression in MCI by rivastigmine or rofecoxib found the annual conversion rate to clinical AD to be less than half of what was predicted (about 5% per year in both). The treatment period in both trials was extended to 4 years in the hope of seeing adequate signal to test [10,12]. None of these trials demonstrated any clear impact on symptom progression in MCI; nevertheless, important lessons learned included the following: the lack of sensitivity of clinical scales developed for AD in MCI, the lack of standardization in MRI acquisition and analysis, the lack of biochemically based disease progression markers, and the need for cognitive tests and performance thresholds that would better identify subjects at risk for the development of AD [13]. Could MRI, cerebrospinal fluid (CSF) markers, or cognitive measurements from one trial be compared with other trials and what sample size was truly needed to detect an effect? Could a biomarker be identified that would more reliably identify people at risk for inclusion in prevention trials than clinical assessments? Although the potential for these treatments to significantly impact disease progression could be questioned, the necessity of understanding how to test reliably for disease progression in AD in a multi-site, registration suitable trial, became clear. As a consequence, clinical scientists within several pharmaceutical companies were quite prepared to examine a means of improving trial methods and assessments and quickly realized that the task was far beyond the means or capability of any one company, and that the endpoints and methods would have to be accepted by the field and health authorities. Assay and process validation are core business tasks for any pharmaceutical company, but even to contemplate validation of in vivo imaging endpoints, with data features in the same order of magnitude of microarray chips and acquisition methods largely mysterious to the drug development world, presented entirely new challenges. This realization provided the attraction for discussions sponsored by the National Institute of Aging and using the Alzheimer's Disease Consortium Study centers to design a study of the progression of illness, using groups of healthy elders, subjects with amnestic MCI, and patients with mild to moderate AD. The subjects were to be followed up for about 3 years (later extended to 5 years in MCI and control cohorts), with serial clinical assessments, biological samples, and imaging; and all the data would be made free and publicly available. For this study, clinical measures would be obtained along with multiple biomarkers to more completely understand their inter-relationships.

Would such a consortium work in a competitive environment, when at least a few companies felt that they were well on the way to developing first-in-class disease modifying treatments? Competition between companies and proprietary interests can be powerful engines for innovation, but can also lead to resistance to public sharing of data or strategy. Would contributing to such an effort bring value to the company or strengthen the competition? Cooperate or defect? To encourage cooperation, it is a credit to the architects of ADNI that the consortium was clearly identified as a precompetitive activity. This principle was accepted and the scope was defined as providing the necessary foundation for clinical trials of disease modification, and to enable broader acceptance of putative candidate biomarkers of disease progression for all involved. Moreover, the fact that an aligned effort would stimulate advancements in the field more swiftly and facilitate acceptance of surrogate endpoints was recognized early in the discussions. A challenge from the management that needed to be addressed was: ''if the data will be free and publically available, and other people will fund ADNI, why should we put in anything?'' Perhaps what was not fully appreciated at the time was how critical active and ongoing participation by industry partners in ADNI would be in selecting the questions to be addressed, identifying methods and assays that could be used in intervention trials, and evaluating how the various measures could demonstrate disease progression. Staying on the sidelines and hoping for the best would have been far less productive. Another initial and rather poignant objection was that several compounds in different treatment classes had already been identified, and some believed that

disease modifying treatments would be registered before ADNI finished. Ten years later, we are a little more humble.

After initial agreement had been reached on the basic design, and at least verbal attestations of willingness to form a consortium had been reached (shepherded by the Foundation for the National Institutes of Health), concerns from industry representatives were solicited and heard. Chief among them was the potential variability between sites with so many exploratory measures being used; this concern was anticipated by the development of rigorous standards of validation of MRI and positron emission tomography (PET) scanners. ADNI began with a focus on volumetric MRI as one of the most widely available and face valid measures of disease progression. The working group leaders were encouraged by industry partners to include a broader spectrum of potential biomarkers, including more extensive fluorodeoxyglucose-positron emission tomography (FDG-PET) and CSF collection. Finally, concern was voiced over the shear ability to complete the task based on the difficulties the Osteoarthritis Initiative experienced meeting timelines. ADNI has been able to achieve its timelines for enrollment and data acquisition, a credit to the commitment of all of the clinical investigators, the working groups, and the extensive and dynamic infrastructure for clinical trial execution that had been developed by Leon Thal and the Alzheimer's Disease Cooperative Study [14].

While drafting the RFP (Request for Proposal) and attempting to identify consensus goals among the many participants, there was a mad race to shore up industry funding - amounting to more than a third of the entire $60MM initial budget - with a few of the most important figures in the clinical study of AD, most notably Leon Thal, taking a leading role in pursuing commitments from various companies. Pfizer had already emerged as a strong advocate for ADNI prompted by discussions in the late 1990s with Michael Weiner. As a neurology consultant to Synarc Inc, an imaging CRO (contract research organization), he had been involved with trials in AD using MRI and was a champion for generation of a normative dataset that could be used as a reference for volumetric change as well as a veteran of the challenges of multi-site MRI imaging. Partly in response to Dr Weiner's proposal for such a reference dataset, Dr Peter J. Snyder, Pfizer's then director for CNS technologies, organized a conference in May 2001 to evaluate the state-of-the-art in neuroimaging as study endpoints in AD trials. While the potential for imaging endpoints was readily identified by the speakers attending that conference, equally profound was the lack of agreement with respect to most all issues raised for discussion, ranging from standardization issues and controls for instrumental error, to the best edge detection algorithms and metrics. A year later, the NIA sponsored a meeting that included representatives from NIA/NIH, academic investigators, the pharmaceutical industry, the imaging equipment industry, FDA, the Alzheimer's Association, and the Institute for the Study of Aging. In a succession of advisory meetings that followed, the basic design, endpoints, and subject selection for ADNI were outlined and the key participants and potential sponsors were identified. Another early partner in this consortium was Lilly Research Labs, and notably Dr Steve Paul. Dr Paul was then vice president for therapeutic area discovery and clinical investigation, a former scientific director for the NIMH intramural research program, and a member of the board of directors of the Foundation for NIH (FNIH). This second early pledge from Lilly led to a domino effect with 8 to 10 other companies promising support soon thereafter.

As the grant was being awarded, Dr Snyder was asked to organize and serve as the first chair of a new Industry Scientific Advisory Board (ISAB), a board that was charged with the dual tasks of maintaining a spirit of collaboration across the industry sponsors; and to assist with scientific leadership and technical expertise for ADNI. In fact, from its inception, the Chair of the ISAB has also served as a regular member on the central Executive Committee for ADNI. The early challenges to the ISAB were substantial, in that the participating pharmaceutical and diagnostic imaging companies had little - if any - prior experience in working together so intensively, and on such a complex, expensive, and potentially valuable scientific discovery program.

Over the course of ADNI, industry has been accepted as a full participant in the design of the study; evaluation of the results; has provided technical resources especially for biomarker analyses; and participates in guiding ongoing analyses of the data as well as undertaking in-house analyses. In fact, two of the four working groups that designed the National Institute of Health request-for-proposals (RFPs) that led to ADNI were actually chaired by representatives from industry (Study Design and Biological Measures). CSF was foreseen by industry representatives as a potentially critical medium for characterizing subjects and monitoring response to treatment, but concerns about the acceptability of lumbar punctures (LP) led to initial projections for LPs in just 20% of subjects. Presentations were made by Industry Scientific Advisory Board (ISAB) members to the ADNI investigators on the importance of CSF samples and support on feasibility came from Washington University (St Louis, MO) investigators. In addition, the ISAB organized and funded the production of a new educational video for study subjects and families, regarding the LP procedure (distributed free of copyright), and featuring Dr Elaine Peskind from the University of Washington in Seattle. This emphasis on the value of the samples and feasibility of the procedure contributed to a three-fold greater collection rate than initially predicted. In addition, the industry contributed internal resource to process and aliquot DNA samples and contributed to add on studies supporting genome-wide association study (GWAS) analysis. The industry has also been instrumental in supporting exploratory biochemical biomarker work and in funding add-on PiB-PET studies More recently, ISAB was instrumental in encouraging Food and Drug Administration consideration of the use of biomarkers in registration trials of treatments targeting progression of AD, including

application in patient selection, as endpoints, and the vetting process that would be required for such biomarkers [15]. Finally, ADNI data are being utilized to develop voluntary submission packages to health agencies to qualify CSF, imaging and cognitive markers as candidate means of identifying subjects at high risk for development of Alzheimer's type dementia for enrollment in early AD clinical trials.

Likewise, contributions from ADNI to clinical trial design and execution by companies have been considerable. MRI and PET center and scanner qualification procedures, and MRI and PET acquisition protocols developed for ADNI have become standards for companies including these measures in Phase 2 and Phase 3 trials in AD. ADNI data are used for determining sample size estimations for clinical trial. The various ''head-to-head'' comparisons of analytic methods are invaluable for reviewing the multiple approaches considered in statistical analysis plans. The engagement of the academic community and regulatory bodies in the ongoing critique of these measures as candidate biomarkers of disease progression provides an important initial step toward the ''validation'' of one or more of these as surrogates.

As promising as these biomarkers appear to be as surrogates for disease progression, implementation in clinical trials as biomarkers of pharmacological action or (hopefully) surrogate clinical endpoints remains a formidable challenge. Validation of biomarkers involves a significant technical component (e.g., assay reliability, reproducibility, robustness) as well as a biological component (e.g., relevance to pharmacology, pathophysiology, and clinical endpoints). As an example, much energy and time was invested before the first MRI scans were collected, including qualification of scanners, regular testing with phantoms, selection and harmonization of sequences across platforms and vendors, followed by rigorous quality control of image data before uploading to the ADNI database. Many of these practices have now been adopted as standards by drug companies using MRI in trials and other academic groups. By way of contrast, ^{11}C-PiB PET imaging was introduced as a promising new technology after enrollment had started; however, methods for characterizing tracer kinetics, optimal acquisition, and methods of analysis were still being discussed [16]. Imaging was limited to centers that could support the tracer synthesis using local adaptations and using a range of cameras and reconstruction methods. How all of this might contribute to variability in the data remains to be determined, but will have to be better understood before this endpoint can achieve technical validation. Availability of not only the data but the ''metadata'' in ADNI: how the scans were obtained and not just how they look will be essential for this task.

Much remains to be done to understand the dynamics and relationship between each form of Aß and turnover between soluble and insoluble forms, to estimate the nature and magnitude of effect that candidate therapeutics need to achieve. As yet, we do not understand how to interpret the changes we observe in the CSF, although progress from Bateman and colleagues in labelling amyloid precursor protein with ^{13}C-leucine may provide an alternate means of establishing full antagonism of Aß formation, even in the presence of some continued concentration of soluble Aß in the CSF [17–19]. We currently depend on semi-quantitative estimates of brain Aß using the Aß PET ligands to explore whether passive immunization using an antibody or active immunization using a vaccine is actually having the desired effect. If a treatment effect can be detected using PET, as suggested by the recent report by Rinne et al,[20] it remains to be established that the ligands bind to the form of Aß that is most related to neuronal loss. Could such imaging be used for dose finding? For example, the current assumption is that the amount of an Aß antibody, whether monoclonal or stimulated by vaccine, that reaches the central compartment and interacts with one or another form of Aß is critical and directly related to the degree of efficacy. There is precedent for using PET to estimate doses with receptor occupancy studies, but most site occupancy modelling is performed for cell surface neurotransmitter receptors using single dose designs and target distribution and volume that are generally well understood. A treatment effect with Aß targeting treatments could take some time; the relationship between the Aß PET ligand signal and Aß protein concentration is poorly understood; and the signal distribution can vary considerably between subjects. Further technical validation of Aß PET imaging and better understanding of the biology of Aß continue to be high on our wish list.

From an industry perspective, we can only confirm what is apparent from the other contributions to this special issue: to date there has been a vast contribution by ADNI to the characterization and technical validation of biomarkers of disease progression in AD. At the same time, it is more apparent that successful development of a treatment that may alter the course of this illness will require continued systematic and multi-faceted examination of patients with Alzheimer's, as well as subjects at risk, to understand how we should evaluate the effects of candidate treatments. Perhaps more importantly, ADNI may help to determine who should be considered as candidates for preventive treatment. The Grand Opportunities grant and proposed ADNI 2 capture this even more completely with the addition of very mildly symptomatic older adults and the opportunity for continued follow-up of the healthy elders from ADNI 1. With the potential availability of therapeutics that may interrupt disease progression and increased appreciation that pathophysiologic changes in AD occur many years before functional loss, finding a reliable means of indentifying subjects at risk when they are mildly symptomatic or even asymptomatic becomes imperative.

At the same time, it must be acknowledged that the majority of therapeutics that have been developed for interrupting disease progression are focused on targeting amyloid processing or deposition. It is a given with a condition as heterogeneous as Alzheimer's disease that other mechanisms will need to be tested. The richness of the ADNI dataset has not

been fully explored and will certainly be challenged to guide us to suitable methods for evaluating the impact of treatments still in the discovery phase.

We have made considerable advances toward validating clinical methods for measuring progression, thanks to the dedication of the ADNI primary and coinvestigators, core leaders, research staff, and patients. The public accessibility of ADNI data, the regular peer review, the presence of the National Institute of Aging as principal sponsor, the Foundation for the National Institutes of Health serving as a ''neutral broker,'' and the distribution of investment and therapeutic interests across multiple companies are critical elements in this effort. The very openness of ADNI and shared participation provide a means of avoiding the conflicts of interest that can plague relationships between individual companies and academic investigators. As we in the industry now consider support of ADNI 2, there should be no doubt of the need to continue to actively collaborate and contribute to this endeavor.

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