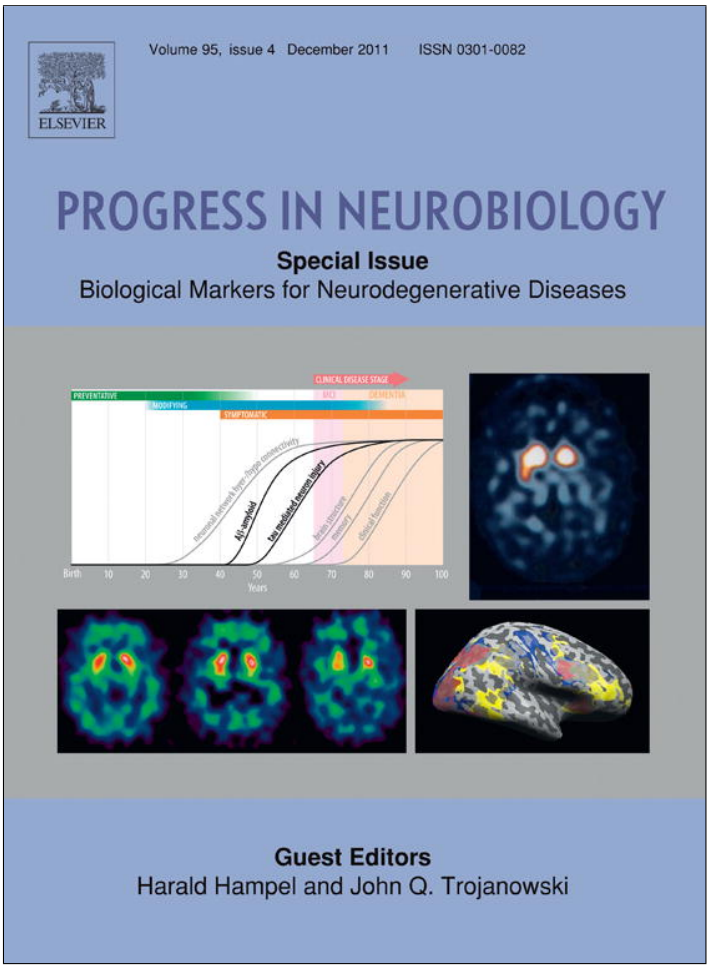

Progress in Neurobiology 95 (2011) 491–495

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Commentary

# Neurodegenerative disease biomarkers: Guideposts for disease prevention through early diagnosis and intervention

John Q. Trojanowski [a,*], Harald Hampel [b,**]

[a] Department of Pathology & Laboratory Medicine, Institute on Aging, Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA
[b] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Goethe-University, Frankfurt, Heinrich-Hoffmann-Str. 10, 60528 Frankfurt, Germany

ARTICLE INFO

*Article history:*
Available online 23 July 2011

*Keywords:*
Biomarkers
Neurodegenerative disease diagnosis
Cerebrospinal fluid
Plasma
Neuroimaging
Disease progression
Clinical testing
Alzheimer's disease
Magnetic resonance imaging
Neuronal network dysfunction

This special issue of **Progress in Neurobiology** entitled "**Biomarkers for Neurodegenerative Disorders**" is a biomarker *tour de force* as a result of the heroic efforts of the experts in research on chemical and neuroimaging biomarkers of neurodegenerative disorders and related diseases who have contributed superb overviews for this very timely volume. The conditions covered in this special issue range from aging related neurodegenerative diseases that now are epidemic such as Alzheimer's disease (AD) and Parkinson's disease (PD), the most common neurodegenerative dementia and movement disorder, respectively, to less common conditions like frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS) and vascular dementia (VaD). Notably, the incidence and prevalence of these disorders are on the rise due to worldwide demographic trends that are leading to rapidly aging populations across the globe (Khachaturian et al., 2009; The Alzheimer's Study Group Report, 2008; Trojanowski et al., 2010a,b; Plassman et al., 2007; Hurd et al., 2007; Wimo and Prince, 2010). Moreover, it is becoming increasingly clear that the hallmark lesions of PD, such as alpha-synuclein inclusions known as Lewy bodies, and those shared by ALS and FTLD such as TDP-43 pathology, co-occur in AD thereby rendering insights into biomarkers of PD, ALS and FTLD equally relevant to developing informative biomarkers for the onset and progression of AD (see Table 1). Further, the clinical and pathological overlap of AD with PD, ALS and FTLD make it attractive to be able to monitor biomarker evidence for the presence of AD pathology in the brains of patients with these other disorders. In addition, this special issue also includes chapters on biomarkers for schizophrenia, affective disorders and multiple sclerosis because the editors of this special issue and the authors of the chapters here envision many opportunities for advances in biomarker research in each of these areas of neuropsychiatric disease research to cross fertilize and stimulate progress in other areas of biomarker research including research on neurodegenerative disease biomarkers.

A leitmotif that emerges from the chapters throughout this special issue is the profound impact that the ongoing "longevity revolution" is having on populations worldwide. In fact, this unprecedented demographic "sea change" represents a seismic shift in populations around the world that is the most powerful driver for nearly all of the disorders covered in this special issue. Indeed, beginning in January of this year, 70 million members of the American "baby boom" generation (i.e. those individuals who were born between 1946 and 1964) started to turn 65 years old, and they will continue to pass this critical lifespan milestone (after which age the incidence of AD rises exponentially to double every 5 years) at a rate of one every 7 s for the next 20 years (Trojanowski et al., 2010a,b; Plassman et al., 2007; Hurd et al., 2007; Wimo and Prince, 2010; Hebert et al., 2001). Moreover, just 20 years from now, in 2031, these baby boomers will begin to turn 85 years old, and it is estimated that among those individuals 85 years of age and older, about 50% will have AD (Trojanowski et al., 2010a,b; Plassman et al., 2007; Hurd et al., 2007; Wimo and Prince, 2010; Hebert et al., 2001). Hence, tor those who have not yet noticed it, the epidemic of aging related neurodegenerative diseases is upon us, and there is no time to lose to forge an international plan to combat this epidemic before it becomes the most socially, economically and medically transformative natural disaster encountered by all populations worldwide to date.

The arguments for a clarion call to take global action to prevent this epidemic or reduce its impact on societies worldwide are straightforward to enumerate, and dramatic demographic changes

* Corresponding author. Tel.: +1 215 662 6399; fax: +1 215 349 5909.
** Corresponding author. Tel: +49 69630187300; fax: +49 69630187303.
*E-mail addresses:* trojanow@mail.med.upenn.edu (J.Q. Trojanowski), harald.hampel@med.uni-frankfurt.de (H. Hampel).

0301-0082/$ – see front matter 
doi:10.1016/j.pneurobio.2011.07.004

**Table 1**
Aging related neurodegenerative diseases characterized by filamentous aggregates of misfolded proteins.

| Disease | Lesions | Components |
|---|---|---|
| Alzheimer's disease (A multi-proteinopathy) | SPs (100%) | Aβ |
| | NFTs (100%) | Tau |
| | LBs (50%) | α-Synuclein |
| | TDP-43 (50%) | TDP-43 |
| Frontotemporal diseases | Inclusions | Tau, TDP-43, FUS |
| Amyotrophic lateral sclerosis | Inclusions | TDP-43, FUS, Tau |
| Parkinson's disease ± Dementia | LBs | α-Synuclein |
| Multiple system atrophy | GCIs | α-Synuclein |
| Prion diseases | SPs | Prions |
| Trinucleotide repeat diseases | Inclusions | Expanded polyglutamine repeats |

This table shows the most common aging related neurodegenerative diseases such as AD and PD, related disorders, as well as other disorders, as well as the hallmark lesions that enable their diagnosis and the peptide/protein building blocks of the pathological signatures of these disorders. As mentioned in the text, the hallmark lesions of PD, such as Lewy bodies, and those shared by ALS and FTLD such as TDP-43 pathology, co-occur in AD. Thus, because of the high percentage of AD patients with alpha-synuclein pathology and TDP-43 lesions, AD is the most common alpha-synucleinopathy and the most common TDP-43 proteinopathy. Hence, biomarkers of PD, ALS and FTLD are highly germane for developing a panel of informative biomarkers for AD as well as for PD, ALS and FTLD.

in the United States exemplify the global trends that have been evolving for over a millennium to culminate in this 21st Century epidemic that is like no other before it. Thus, due to the current global "longevity revolution", life expectancy in the United States continues to increase, and there is substantive good news about the quality of health and functioning of the elderly population in the United States. For example, data from the 1982–2004 National Long-Term Care Survey suggest that chronic disability prevalence is decreasing at a rate of just above 2% per year for those over age 65 in the years between 1999 and 2004 (Manton, 2008). Many factors account for this, but most evidence points to the improving health of this segment of the population (Manton, 2008). However, this positive news notwithstanding, there are increasing concerns about the impact of aging related diseases and especially aging related neurodegenerative disorders like AD on the growing number of individuals entering the 7th decade of life and beyond (Plassman et al., 2007; Hurd et al., 2007; Wimo and Prince, 2010; Hebert et al., 2001). The estimates on the prevalence of AD in the United States vary but current data indicate that there are 5.3 million Americans with AD (Wimo and Prince, 2010). Regardless of variations on these estimates of the burden of AD in the United States, Europe, Africa, Australia, Asia and elsewhere, the number of people with AD is expected to explode soon as the global population ages, unless ways to prevent or treat the disease are found very soon. Indeed, a new person develops AD in the United States approximately every 70 s, and AD has recently displaced diabetes as the 6th leading cause of death in the United States (Wimo and Prince, 2010). By 2030, as many as 7.7 million people in the United States alone could have AD, and by 2050 this number could rise to around 11–16 million people (Trojanowski et al., 2010a,b; Plassman et al., 2007; Hurd et al., 2007; Wimo and Prince, 2010; Hebert et al., 2001). It is currently estimated that the cost of AD in the United States exceeds US $150 billion annually, and AD will affect the economies of other countries to a similar extent, including developing nations (Wimo and Prince, 2010). For example, the London-based Alzheimer's Disease International (ADI) has determined that in the next 30 years the number of AD patients will more than quadruple in India, China and other countries in Asia, Australasia and Oceania from approximately 16 million now in 2010 to ~61 million by 2050 (Wimo and Prince, 2010). Further, in Africa there is expected to be >8 million AD patients by 2050 and the worldwide burden of AD will be >115 million patients by this time (Wimo and Prince, 2010). Although at first the global explosion of AD patients may appear to be a far too overwhelming a challenge to contemplate overcoming in the near term or by 2050, it is important to realize it is estimated that a "cure" for AD is not essential to have a highly significant impact on this disorder since delaying the onset by just 5 years could reduce the incidence and prevalence as well as the cost of AD by 50% between now and 2050 (Brookmeyer et al., 1997).

Thus, with the total worldwide costs of dementia estimated to be US $604 billion in 2010 (with 70% of these expenditures for dementia care occurring in Europe and North America), these costs account for around 1% of the world's gross domestic product (Wimo and Prince, 2010). Accordingly, if dementia care was a country, it would be the world's 18th largest economy, and if it were a company, it would be the world's largest exceeding Wal-Mart (US $414 billion) and Exxon Mobil (US $311 billion) in expenditures (Wimo and Prince, 2010). Given these economic realities, ADI has called for governments and other major research funders to act now to increase dementia research funding, including research into prevention, to a level more proportionate to the economic burden of AD and related disorders (Wimo and Prince, 2010). To that end, ADI points to data suggesting that a 15-fold increase in funding for dementia is required to reach parity with research into heart disease, and a 30-fold increase is needed to achieve parity with cancer research (Wimo and Prince, 2010).

While the chapters here describe impressive progress in biomarker research for each of the disorders mentioned above, there is no doubt that AD biomarker research is the most advanced at this time for reasons that will become evident below. As noted above, AD is the most common dementia (Khachaturian et al., 2009; The Alzheimer's Study Group Report, 2008; Trojanowski et al., 2010a,b; Plassman et al., 2007; Hurd et al., 2007; Wimo and Prince, 2010; Hebert et al., 2001; Schneider et al., 2007; White et al., 2005), and the hallmark lesions of AD are Aβ plaques and neurofibrillary tangles (NFTs) formed by abnormal tau. Clinical symptoms in AD patients relate more closely to NFTs, neurodegeneration and synapse loss than to Aβ deposits (Gomez-Isla et al., 1997; Savva et al., 2009; Terry et al., 1991). AD can be divided into a pre-symptomatic phase in which subjects are cognitively normal but have AD pathology, a prodromal phase known as mild cognitive impairment (MCI) and a third phase when patients show evidence of clinical dementia with impairments in multiple domains and loss of the ability to carry out activities of daily living (Knopman et al., 2003; Price and Morris, 1999; Petersen, 2004). It has been suggested that diagnostic criteria for early AD should be redefined by the presence of memory impairments plus biomarker evidence of AD pathology, although the diagnosis of definite AD still requires an autopsy with postmortem examination of the brain to identify AD neuropathology (Dubois et al., 2010). However, it is critical to identify the beginning stages of AD well before clinical symptom onset to optimize potential efficacy of disease modifying therapies, as well as to enable drug development aimed at AD prevention (Hampel et al., 2010, 2011a). Indeed, data emerging from the North American Alzheimer's Disease

Neuroimaging Initiative (ADNI) funded by National Institutes of Health (NIH), especially the National Institute on Aging (NIA) of the NIH, as well as by numerous pharmaceutical companies, foundations and other NIA partners in this effort (see acknowledgements for details), suggest that success in accomplishing this may be close at hand (Aisen et al., 2010; Trojanowski et al., 2010a,b; Weiner et al., 2010). This sense of optimism is based on a recently proposed hypothetical model (Jack et al., 2010) for the temporal ordering of biomarkers of AD pathology that emerged from the initial funding period of ADNI (ADNI-1), which formally began in 2004, and this model will be refined and tested further in the renewal period of ADNI (ADNI-2) that began in 2010 to extend through to 2015.

Briefly, the model proposed by ADNI investigators (see Fig. 1) is based on the view that AD begins with abnormal processing of amyloid precursor protein thereby increasing brain Aβ levels which leads to neuron dysfunction and death (Jack et al., 2010). The model also assumes a lag phase between the onset of Aβ deposition and progressive neuron loss, while also acknowledging that differences in brain plasticity or other factors likely account for the variable duration of this lag phase among different individuals with similar burdens of AD pathologies. The presence of additional brain pathologies (e.g. alpha-synuclein inclusions, TDP-43 lesions, VaD pathologies) also may contribute to clinical variations in AD patients. Briefly, the hypothetical model proposed by ADNI investigators in Fig. 1 relates AD onset and progression to AD biomarkers based on the following assumptions: (1) these biomarkers become abnormal before the manifestation of clinical symptoms begins; (2) Aβ biomarkers become abnormal first, followed by changes in tau and neurodegenerative biomarkers; (3) tau and neurodegenerative biomarkers correlate more closely than Aβ with clinical disease severity; (4) Aβ, tau and neurodegenerative biomarkers can be temporally ordered to reflect stages in the onset and progression of AD. Growing evidence supports these assumptions as reviewed recently in Jack et al. (2010), and this model will be tested more rigorously in ADNI-2 as well as by the efforts of other biomarker researchers across the globe who are

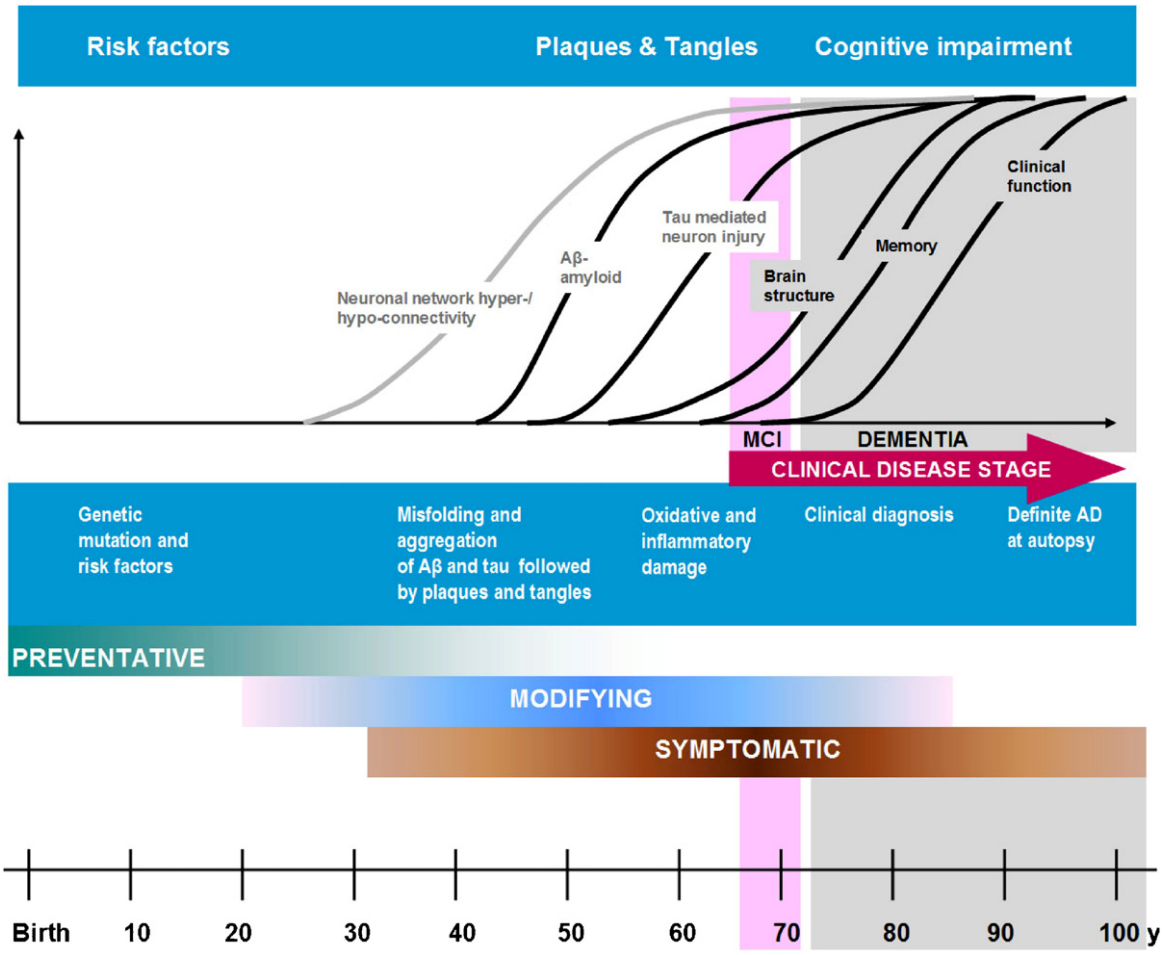


**Fig. 1.** This figure shows a hypothetical time line for the onset and progression of AD neurodegeneration and cognitive impairments progressing from NC to MCI and on to AD. The only highly predictive biomarkers for AD years before disease onset are genetic mutations that are pathogenic for familial AD (FAD), and these can be detected from gestation onwards to identify those individuals in FAD kindreds who will go on to develop AD later in life. However, the emphasis in this introduction to this special issue is on promising chemical and imaging biomarkers studied in ADNI for the diagnosis of AD and predicting conversion from NC and/or MCI status to AD. Age from birth onwards is indicated in the timeline at the bottom of the figure and the green, blue and brown bars indicate the time points at which preventative, disease modifying and symptomatic interventions, respectively, are likely to be most effective, and the aqua bars identify milestones in the pathobiology of AD that culminate in clinical disease, death and autopsy confirmation of AD. However, AD biomarkers are needed to accelerate efforts to test the efficacy of preventative and disease modifying therapies for AD. To do this, it is important to determine the temporal ordering of AD biomarkers, and the proposed extended ADNI model illustrating the ordering of biomarkers of AD pathology relative to stages in the clinical onset and progression of AD is shown in the upper half of this figure. In the insert, clinical disease is on the horizontal axis and it is divided into three stages i.e. normal cognitive status to the left of MCI followed by AD dementia to the right of MCI. The vertical axis indicates the range from normal to abnormal for each of the biomarkers as well as for measures of memory and functional impairments. Amyloid imaging and CSF Aβ are biomarkers of brain Aβ amyloidosis. CSF tau and FDG PET are biomarkers of neuron injury and degeneration while structural MRI is a biomarker of abnormal brain morphology. Functional MRI is used to detect aberrant neuronal activation and network interconnectivity patterns and although data on the timing of the abnormalities in neuronal network activation are still emerging, we insert this change as a possible very early biomarker, but more studies are needed to define the timing of these changes.

part of a World Wide ADNI (WW-ADNI) network of collaborating programs involving ADNI-like projects in Europe, Japan, Australia, China and Korea (Trojanowski et al., 2010a,b). Thus, by implementing the goals of ADNI-2 and WW-ADNI, it will be possible to advance understanding of the applications of validated and new AD biomarkers as predictive, diagnostic and progression markers for persons transitioning from normal control (NC) to early MCI/late MCI and thence to AD. A promising emerging complementary extension to Aβ- and neurodegeneration biomarkers seems to be aberrant functional brain activation and neuronal network interconnectivity patterns in disorders of the brain, particularly neurodegenerative diseases. These biomarker changes are not only observed in presymptomatic individuals harboring increased brain amyloid burden (Hedden et al., 2009), but also in genetic risk carriers of younger age (20–35 years), which are presumably several decades away prior to the onset of possible clinical symptoms (reviewed in Hampel et al., 2010 and in Prvulovic et al., 2011). These dynamic functional imaging biomarkers may even allow clinicians and researchers to detect pre-amyloidogenic stages and functional endophenotypes of AD (Sheline et al., 2010) and thus greatly extend the time-frame preceding other neurochemical markers and clinical onset of dementia. Importantly, this will allow for the application of preventive measures at the earliest and potentially fully reversible stages of disease inception. Moreover, functional neuroimaging may offer potentially unprecedented possibilities to develop mechanism independent surrogate markers that will serve to accurately predict clinical outcome in interventional trials and AD drug development (Hampel et al., 2011b; Ewers et al., 2011). Of note, while backed up by substantial and ever growing body of evidence, these functional neuroimaging markers await confirmation and validation from longitudinal studies as well as from clinicopathological studies with autopsy-verified diagnosis.

Significantly, the staging of AD biomarkers and defining their temporal relationships with the phases of AD present opportunities to test AD biomarker hypotheses by ADNI and other investigators who mine ADNI data or develop their own biomarker data sets in WW-ADNI or other biomarker initiatives. In addition to their use in diagnostic tests, chemical and neuroimaging biomarkers will become increasingly valuable in clinical trials, for enrichment of patient samples with pure AD cases, for patient stratification, as safety markers, and to detect and monitor the biochemical effects of drugs as well as whether or not they engage their intended targets. Thus, in the very near future, we expect that data emerging from North American ADNI, WW-ADNI and other biomarker initiatives will deliver on the promise of these programs to provide validated AD biomarkers for a wide variety of applications including predictive testing for AD, diagnosis of AD and for use in clinical trials to assess the response of disease modifying therapies in AD patients. Indeed, biomarkers may make it possible to diagnose definitive AD prior to death so that biomarkers can replace the autopsy as the "gold standard" for the diagnosis of definitive AD in living patients (Blennow et al., 2010; Shaw et al., 2011).

One of many examples of the advances of the WW-ADNI effort is the report on reliability and feasibility data of the European-ADNI (E-ADNI) biological marker program led by Harald Hampel and Kaj Blennow. One of the methodological insights of the study program was that the use of frozen rather than fresh samples renders higher diagnostic accuracy within a multicenter context (Buerger et al., 2009). Moreover, this study demonstrated that the cooperation between different European expert academic centers within international multi-center MCI and AD studies is feasible, and that cooperative sample processing, data collection and analysis is not only reliable, but also offers a most promising chance for groups across the world's continents and research environments to team up into the huge WW-ADNI effort.

Finally, the amazing advances in AD biomarkers summarized here and other chapters in this volume bode very well for similar advances in biomarker research for the other disorders summarized in this special issue. Indeed, the chapter by Marek and collaborators in the Parkinson Progression Marker Initiative (PPMI), which is funded by the Michael J. Fox Foundation and several other partners including a number of pharmaceutical companies, demonstrates how the ADNI model can be applied to other neurodegenerative disorders. Thus, there is every reason to be optimistic that PPMI will succeed like ADNI in having a powerful effect on improving the diagnosis of PD as well as the design of clinical trials to test novel therapies for PD by exploiting advances in PD biomarker research promoted by PPMI.

## Acknowledgements

We thank our North American ADNI and WW-ADNI colleagues for their contributions to the work summarized here. ADNI is funded by the National Institute on Aging (AG24904), the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co. Inc., Novartis AG, Pfizer Inc., F. Hoffman-La Roche, Schering-Plough, Synarc Inc., and Wyeth, as well as non-profit partners including the Alzheimer's Association and the Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org/). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for NeuroImaging at the University of California, Los Angeles. This research was also supported by AG10124 and the Marian S. Ware Alzheimer Program as well as by the Neuronal Coordination Research Focus Frankfurt (NeFF), Neurodegeneration Branch, Alzheimer's Disease Project (led by H.H.). J.Q.T. is the William Maul Measy-Truman G. Schnabel Jr. M.D. Professor of Geriatric Medicine and Gerontology. We thank all the patients and their families who participate in biomarker research and make possible the progress summarized here.

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