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Testing the Right Target and the Right Drug at the Right Stage

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Abstract

Alzheimer's disease (AD) is the only leading cause of death for which no disease-modifying therapy is currently available. Recent disappointing trial results at the dementia stage of AD have raised multiple questions about our current approaches to the development of disease-modifying agents. Converging evidence suggests that the pathophysiological process of AD begins many years before the onset of dementia. So why do we keep testing drugs aimed at the initial stages of the disease process in patients at the end-stage of the illness?

Alzheimer's disease (AD) remains one of the most feared consequences of aging, affecting more than one out of every ten individuals over the age of 65. With more than 10,000 baby boomers turning 65 every day in the United States alone, we are truly facing an AD epidemic. Over the past decade, a string of disappointing clinical trial results have raised concerns about our current strategy for development of AD-modifying therapies. Three hypotheses can explain these recent AD trial failures: (i) We are targeting the wrong pathophysiological mechanisms; (ii) The drugs do not engage the intended targets in patients; and (iii) The drugs are hitting the right targets, but are doing so at the wrong stage of the disease. Here, we address the third supposition and suggest that specific amyloid-based therapies be directed at much earlier stages of AD perhaps even prior to the emergence of clinical symptoms. Furthermore, we argue that the field has sufficient tools to begin "secondary prevention" trials in asymptomatic individuals who are at high risk for progression to cognitive impairment and AD dementia.

THE RIGHT TARGETS?

The majority of current AD clinical trials target brain amyloid accumulation, and the recent trial failures have been viewed by some as "nails in the coffin" of the amyloid hypothesis (1). In contrast, mounting evidence from natural history studies supports amyloid- β (A β) accumulation in brain as an early biomarker and critical event in the early progression of AD. Nearly all of the major genetic risk factors of AD also point toward A β accumulation as a critical pathogenic factor in the disease. Multiple studies based on cerebrospinal fluid (CSF) assays or imaging of brain amyloid with positron emission tomography (PET) in human subjects suffering from mild cognitive impairment (MCI) now suggest that positive amyloid markers confer a three to fivefold higher likelihood of progression to AD dementia (2–9). Similarly, recent studies from presymptomatic subjects who carry deterministic autosomal dominantly inherited mutations, such as mutations in the genes that encode presenilin-1, presenilin-2, or amyloid precursor peptide (APP), have demonstrated evidence of A β accumulation in the brain beginning at least a decade before the predicted age of onset for dementia, accompanied by evidence of "downstream" markers of neuronal injury (for

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example, tau and phospho-tau proteins in the cerebrospinal fluid (CSF), functional imaging alterations, atrophy and cortical thinning seen by volumetric magnetic resonance imaging (MRI) (10, 11). Consonant with these findings in genetic at-risk populations are multiple recent reports of an AD-like “endophenotype”, that is a pattern of abnormalities seen on functional and structural imaging markers, detected in clinically normal amyloid-positive older individuals (12–17). A few studies have also reported that, even within the range of normal cognitive performance for age, greater amyloid burden is associated with subtle decreases in performance on neuropsychological tests and that these amyloid-positive normal individuals have a significantly greater risk of cognitive decline (18–24).

However, the consistent reports of amyloid positivity in one-third of the normal older population has been interpreted as a double-edged sword for the amyloid hypothesis, as how do older individuals spend years with a “head full of amyloid” and remain apparently healthy? Indeed, the clinical implication of brain amyloidosis, in clinically normal older individuals, is one of the crucial outstanding questions in AD research. Two types of investigations are required to disambiguate this conundrum. First, we need decades-long cohort studies of aging that are rich in sensitive cognitive, clinical, and biomarker assessments to elucidate the trajectories and relations among various markers of AD pathology and symptom progression. Second, we need studies of effective anti-amyloid therapies to determine whether early intervention in the process of amyloid accumulation will alter long-term cognitive and clinical outcomes in these asymptomatic subjects.

THE RIGHT DRUGS?

The results of clinical trials with a number of agents that target the reduction of amyloid burden (see Table 1) have indeed been discouraging at the stages of mild to moderate dementia. Tramiprosate, a glycosaminoglycan mimetic that was thought to block aggregation of A β in vitro was moved into large clinical trials after a small Phase II study suggested that the drug also reduced A β ₄₂ peptide concentrations in the CSF of AD patients with mild to moderate dementia. The pivotal trial results failed to demonstrate efficacy with respect to improvements in cognitive or functional outcome measures. Tarenflurbil, a nonsteroidal antiinflammatory drug shown to have γ -secretase activity in vitro and in transgenic mice models of AD, entered Phase III clinical trials without clear evidence of central nervous system (CNS) target engagement in humans. Unfortunately, the trials also failed to support efficacy in AD dementia patients. Most recently, the Phase III development program for semagacestat, a γ -secretase inhibitor, was halted early because of adverse effects on cognition (and other safety concerns) in AD dementia patients. This result was particularly discouraging to the AD field, as semagacestat had the strongest Phase II evidence to date of CNS target engagement, with clear dose-related reduction in A β ₄₂ peptide generation in CSF (25). Recent reports of small studies with monoclonal antibodies against A β have shown a reduction in fibrillar (or plaque) A β burden in AD patients, as quantified by ¹¹C PIB-PET (Pittsburg Imaging Compound B Positron Emission Tomography) imaging (26, 27); however, thus far, this reduction has not correlated with any clear clinical benefit in the limited number of patients treated at the stage of mild to moderate dementia. A very small number of autopsies performed on brain tissue from AD patients who demonstrated evidence of antibody response to responded to active immunization with AN-1792, a vaccine against the A β peptide, demonstrated evidence of plaque clearance but no apparent effect on the clinical course of their dementia, as measured by cognitive and functional outcomes (28).

THE RIGHT STAGE??

A number of trials of promising agents are ongoing in AD patients who are at the stage of mild-to-moderate dementia, and we hope that these studies will demonstrate some evidence of therapeutic efficacy. However, the lack of clinical benefit seen in the aforementioned clinical studies raises the possibility that we are attempting intervention too late in the course of the disease, especially with anti-A β therapy. Several pharmaceutical companies have begun Phase II testing of therapeutic agents in patients who are at the prodementia (prodromal) stage of AD, which is defined by clinical symptoms of mild cognitive impairment (MCI) combined with evidence of amyloid accumulation in the brain, as assessed by CSF or PET amyloid imaging. -But intervention at this stage also may be too late. Recent hypothetical models, based on the available biomarker data available to date, suggest that A β accumulates for well over a decade and the neurodegeneration that occurs downstream of A β accumulation is well entrenched even prior to MCI (29, 30). Therefore, it is possible that treatments that remove all toxic A β species from the brain still will not alter the clinical course of the disease after significant neuronal injury. Triple-transgenic mousemodels suggest anti-A β intervention is unlikely to succeed once neurodegeneration is well established (31). Indeed, some researchers have postulated that later stages of the AD pathophysiologic process may become increasingly independent from the toxic effects of A β , such that other mechanisms such as calcium dyshomeostasis, tau-mediated neurodegeneration, and mitochondrial dysfunction predominate (32). This line of thinking has been controversial, as clearly there is evidence of deteriorating synaptic function and ongoing neuronal loss throughout the course of AD dementia; thus one might argue that a biologically active treatment for AD should demonstrate efficacy at all stages of the illness. However, there is analogous evidence for stage-dependent treatment success in other chronic diseases, such as cancer or cardiovascular disease. Lowering of serum cholesterol reduces morbidity and mortality if administered prior to or after a single myocardial infarction, but has very little effect if administered at the stage of congestive heart failure that results from coronary artery disease when the myocardium is irreversibly damaged. If more than 50% of critical neurons in the medial temporal lobe memory circuits are already lost by the MCI stage of AD (33), it seems unlikely that we could fully rescue memory function at the dementia stage of AD.

Therefore, the accumulated evidence suggests that researchers begin to (i) target selected therapies to specific stages of AD and (ii) think about the disease in terms of primary, secondary, and tertiary prevention rather than lumping together all disease-modifying treatments across the disease spectrum (Fig. 1). Although primary prevention would be ideal, the prospect of large primary prevention trials for late-onset sporadic AD remains daunting and likely unfeasible given the length of treatment required to achieve a clinical endpoint. Furthermore, there is considerable concern over the cost and safety of treating thousands of individuals who may never develop AD pathology. At present, the earliest feasible stage for therapeutic trials in sporadic AD is likely to be at the stage of asymptomatic amyloid accumulation, based on the (still unproven) hypothesis that brain amyloidosis is indeed indicative of early-stage AD. These studies may be considered “secondary prevention” trials, aimed at preventing or slowing the progression of the clinical syndrome in those in whom the pathophysiological process of AD has already begun.

ARE SECONDARY PREVENTION TRIALS FEASIBLE?

A number of secondary prevention trial initiatives are already in the planning stages for several at-risk populations: (i) Individuals who carry autosomal dominant mutations, a very small population (less than 2% of all AD) with virtually 100% likelihood of early-onset AD dementia; (ii) individuals who are homozygous for the *APOE* $\epsilon 4$ allele, a somewhat larger

population with a less-certain risk of clinical progression and a potentially increased risk of amyloid-related imaging abnormalities (ARIA), as suggested by recent findings in ongoing trials (34); and (iii) asymptomatic amyloid-positive older individuals at risk by virtue of advanced age, the largest target population for eventual secondary prevention therapy, but with relatively little long-term data to determine the risk of progression on an individual basis.

Recent longitudinal data from natural history studies suggest that it is now feasible to conduct secondary prevention trials over a time-frame (3 to 5 years) that is realistic for clinical trials that require frequent visits for safety monitoring, but there are important trial-design considerations. In particular, it is likely that regulatory authorities will require evidence of an effect on a cognitive or clinical outcome, in addition to evidence of biomarker response. Thus, the best chance of detecting efficacy may depend on defining a relatively homogeneous population of subjects who will demonstrate evidence of clinical progression during this relatively short time-frame, but who are not at a clinical disease stage at which it is too late to intervene with anti-amyloid therapy. Individuals who show evidence of amyloidosis and neurodegeneration on biomarker and imaging studies, and perhaps very subtle cognitive symptoms (Stage 3 of the recently proposed National Institute on Aging-Alzheimer's Association framework for preclinical/presymptomatic stages of AD) (35) may be mostly likely to demonstrate clinical decline toward MCI and dementia over a few years time, but intervention at this stage might be suboptimal for slowing disease progression with an amyloid-modifying therapeutic agent alone.

These secondary prevention trials should embed a variety of fluid biomarkers and imaging measures to help determine whether decreasing amyloid burden can slow downstream neurodegeneration, and whether the success of anti-amyloid therapy is dependent on the degree of neurodegeneration at baseline. Unfortunately, although a number of these biomarkers have shown great promise at identifying individuals at-risk for progression, the use of biomarkers to track therapeutic response has been rather problematic. The most well-known example of a paradoxical biomarker response is the magnetic resonance imaging (MRI) results from the AN-1792 vaccine trial. Individuals who mounted an immune response to anti-A β vaccination showed greater rates of brain shrinkage despite some evidence of modest cognitive benefit on a subset of memory measures (36). As mentioned above, the semagacestat Phase II trials demonstrated a decrease in CSF A β ₄₂, but it remains unclear whether an increase or decrease in this biomarker is associated with therapeutic benefit. For immunotherapy agents, such as monoclonal antibodies and newer vaccine approaches, aimed at reducing fibrillar A β burden, PET amyloid imaging may be the best marker of target engagement (26), but it remains unknown to what extent reduction in fibrillar A β is indicative of decreases in other potentially more-toxic forms of A β . These results from recent clinical trials underscore the need to better characterize the “theragnostic” response of multiple biomarkers in these early AD trials.

Perhaps the most daunting challenge is to identify a clinically relevant change that defines the stage at which an individual tips from cognitively normal to abnormal which may be years before a formal diagnosis of MCI is made. The cognitive measures that may be most sensitive to the very earliest symptomatic phases of AD are likely to differ from those currently used in trials with subjects who are in the late MCI and AD dementia stages (22, 23). Moreover, clinical decline is thought to be nonlinear over the course of AD, such that cognitive decline is most rapid and most easily detected (at least with current tools) during the moderate stages of dementia. Indeed, researchers and patients are caught on the “horns of a dilemma,” because the most efficacious time for intervention with currently available anti-amyloid therapies may be early in the early pathophysiological stages of AD, but this is also the stage at which it will be particularly difficult to detect clinical decline over a short

time-frame. Although a number of studies have demonstrated evidence of subtle cognitive decline in amyloid-positive normal individuals (21, 23, 24), it remains unknown whether measuring change in a single domain, such as episodic memory, or a newly developed composite measure will be most useful for tracking very early progression that is specific to AD-related pathology.

Even with well-characterized at-risk populations, better-validated biomarkers, and more sensitive clinical measures, prevention trials are likely to be expensive, and partnerships between academia, government, industry, and philanthropic organizations will be required to fund these efforts. However, the expense of these prevention studies will pale in comparison to the cost of caring for an ever-expanding number of AD dementia patients if we do not find a successful disease-modifying therapy. Finally, there are important ethical considerations in planning these secondary prevention trials. The enrollment process for such trials may require researchers to reveal the results of biomarker and/or genetic screening to subjects. Given the incomplete knowledge to date, it will be difficult but crucial to explain the uncertainty regarding the likelihood that a clinically normal individual with high amyloid burden will indeed progress toward AD dementia. In addition, on the basis of results with the current set of drugs being tested in large-scale clinical trials, it is likely that biologically active medications will carry some risk. We must decide if it is reasonable to expose asymptomatic individuals to drugs with a small but significant risk of adverse events, even if some of them will not develop the clinical symptoms of AD. If we can better assess the risks for an individual participant, these cognitively intact individuals can make an informed decision, which some would argue is more ethical than our current practice of asking patients with mild dementia to fully assess the risk-benefit ratios. The potential benefits to society are high, and we believe that many individuals will volunteer for these studies in the hope that their children's generation will see AD dementia as a preventable illness.

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Competing interests

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References and Notes

1. Selkoe DJ. Resolving controversies on the path to Alzheimer's therapeutics. *Nat Med.* 2011; 17:1060–1065. [PubMed: 21900936]
2. Brys M, Pirraglia E, Rich K, Rolstad S, Mosconi L, Switalski R, Glodzik-Sobanska L, De Santi S, Zinkowski R, Mehta P, Pratico D, Saint Louis LA, Wallin A, Blennow K, de Leon MJ. Prediction and longitudinal study of CSF biomarkers in mild cognitive impairment. *Neurobiol Aging.* 2009; 30:682–690. [PubMed: 17889968]
3. Forsberg A, Engler H, Almkvist O, Blomquist G, Hagman G, Wall A, Ringheim A, Langstrom B, Nordberg A. PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging.* 2008; 29:1456–1465. [PubMed: 17499392]

4. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol.* 2006; 5:228–234. [PubMed: 16488378]
5. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, Herukka SK, van der Flier WM, Blankenstein MA, Ewers M, Rich K, Kaiser E, Verbeek M, Tsolaki M, Mulugeta E, Rosen E, Aarsland D, Visser PJ, Schroder J, Marcusson J, de Leon M, Hampel H, Scheltens P, Pirttila T, Wallin A, Jonhagen ME, Minthon L, Winblad B, Blennow K. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA.* 2009; 302:385–393. [PubMed: 19622817]
6. Visser PJ, Verhey F, Knol DL, Scheltens P, Wahlund LO, Freund-Levi Y, Tsolaki M, Minthon L, Wallin AK, Hampel H, Burger K, Pirttila T, Soininen H, Rikkert MO, Verbeek MM, Spira L, Blennow K. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol.* 2009; 8:619–627. [PubMed: 19523877]
7. Wolk DA, Price JC, Saxton JA, Snitz BE, James JA, Lopez OL, Aizenstein HJ, Cohen AD, Weissfeld LA, Mathis CA, Klunk WE, De-Kosky ST. Amyloid imaging in mild cognitive impairment subtypes. *Ann Neurol.* 2009; 65:557–568. [PubMed: 19475670]
8. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, Knopman DS, Petersen RC, Jack CR Jr. MRI and CSF biomarkers in normal, MCI, and AD subjects: diagnostic discrimination and cognitive correlations. *Neurology.* 2009; 73:287–293. [PubMed: 19636048]
9. Jack CR Jr, Wiste HJ, Vemuri P, Weigand SD, Senjem ML, Zeng G, Bernstein MA, Gunter JL, Pankratz VS, Aisen PS, Weiner MW, Petersen RC, Shaw LM, Trojanowski JQ, Knopman DS. Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain.* 2010; 133:3336–3348. [PubMed: 20935035]
10. Ringman JM, Younkin SG, Pratico D, Seltzer W, Cole GM, Geschwind DH, Rodriguez-Agudelo Y, Schaffer B, Fein J, Sokolow S, Rosario ER, Gyls KH, Varpetian A, Medina LD, Cummings JL. Biochemical markers in persons with preclinical familial Alzheimer disease. *Neurology.* 2008; 71:85–92. [PubMed: 18509095]
11. Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, Ringman JM, Salloway S, Sperling RA, Windisch M, Xiong C. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther.* 2011; 3:1. [PubMed: 21211070]
12. Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, Koeppe RA, Mathis CA, Weiner MW, Jagust WJ. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain.* 2009; 132:1310–1323. [PubMed: 19042931]
13. Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, Shiung MM, Gunter JL, Boeve BF, Kemp BJ, Weiner M, Petersen RC. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain.* 2009; 132:1355–1365. [PubMed: 19339253]
14. Sperling RA, Laviolette PS, O'Keefe K, O'Brien J, Rentz DM, Pihlajamaki M, Marshall G, Hyman BT, Selkoe DJ, Hedden T, Buckner RL, Becker JA, Johnson KA. Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron.* 2009; 63:178–188. [PubMed: 19640477]
15. Becker JA, Hedden T, Carmasin J, Maye J, Rentz DM, Putcha D, Fischl B, Greve DN, Marshall GA, Salloway S, Marks D, Buckner RL, Sperling RA, Johnson KA. Amyloid-beta associated cortical thinning in clinically normal elderly. *Ann Neurol.* 2011
16. Schott JM, Bartlett JW, Fox NC, Barnes J. Increased brain atrophy rates in cognitively normal older adults with low cerebrospinal fluid Aβ₄₂. *Ann Neurol.* 2010; 68:825–834. [PubMed: 21181717]
17. Jack CR Jr, Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, Ivnik RJ, Roberts RO, Rocca WA, Boeve BF, Petersen RC. An operational approach to NIA-AA criteria for preclinical Alzheimer's disease. *Annals of Neurology.* 2011 e-pub.
18. Skoog I, Davidsson P, Aevansson O, Vanderstichele H, Vanmechelen E, Blennow K. Cerebrospinal fluid beta-amyloid 42 is reduced before the onset of sporadic dementia: a

- population-based study in 85-year-olds. *Dement Geriatr Cogn Disord*. 2003; 15:169–176. [PubMed: 12584433]
19. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol*. 2007; 64:343–349. [PubMed: 17210801]
 20. Li G, Sokal I, Quinn JF, Leverenz JB, Brodey M, Schellenberg GD, Kaye JA, Raskind MA, Zhang J, Peskind ER, Montine TJ. CSF tau/Abeta42 ratio for increased risk of mild cognitive impairment: a follow-up study. *Neurology*. 2007; 69:631–639. [PubMed: 17698783]
 21. Morris JC, Roe CM, Grant EA, Head D, Storandt M, Goate AM, Fagan AM, Holtzman DM, Mintun MA. Pittsburgh Compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. *Arch Neurol*. 2009; 66:1469–1475. [PubMed: 20008650]
 22. Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA. Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol*. 2010; 67:353–364. [PubMed: 20373347]
 23. Darby DG, Brodtmann A, Pietrzak RH, Fredrickson J, Woodward M, Villemagne VL, Fredrickson A, Maruff P, Rowe C. Episodic Memory Decline Predicts Cortical Amyloid Status in Community-Dwelling Older Adults. *J Alzheimers Dis*. 2011
 24. Villemagne VL, Pike KE, Chetelat G, Ellis KA, Mulligan RS, Bourgeat P, Ackermann U, Jones G, Szeke C, Salvado O, Martins R, O'Keefe G, Mathis CA, Klunk WE, Ames D, Masters CL, Rowe CC. Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. *Ann Neurol*. 2011; 69:181–192. [PubMed: 21280088]
 25. Bateman RJ, Siemers ER, Mawuenyega KG, Wen G, Browning KR, Sigurdson WC, Yarasheski KE, Friedrich SW, Demattos RB, May PC, Paul SM, Holtzman DM. A gamma-secretase inhibitor decreases amyloid-beta production in the central nervous system. *Ann Neurol*. 2009; 66:48–54. [PubMed: 19360898]
 26. Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, Mathis CA, Blennow K, Barakos J, Okello AA, Rodriguez Martinez de Liano S, Liu E, Koller M, Gregg KM, Schenk D, Black R, Grundman M. 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol*. 2010; 9:363–372. [PubMed: 20189881]
 27. Ostrowitzki S, Depta D, Thurfjell L, Barkhof F, Bohrmann B, Brooks DJ, Klunk WE, Ashford E, Yoo K, Xu ZX, Loetscher H, Santarelli L. Mechanism of Amyloid Removal in Patients With Alzheimer Disease Treated With Gantenerumab. *Arch Neurol*. 2011
 28. Nicoll JA, Barton E, Boche D, Neal JW, Ferrer I, Thompson P, Vlachouli C, Wilkinson D, Bayer A, Games D, Seubert P, Schenk D, Holmes C. Abeta species removal after abeta42 immunization. *J Neuropathol Exp Neurol*. 2006; 65:1040–1048. [PubMed: 17086100]
 29. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9:119–128. [PubMed: 20083042]
 30. Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, Frapp J, Tochon-Danguy H, Morandau L, O'Keefe G, Price R, Raniga P, Robins P, Acosta O, Lenzo N, Szeke C, Salvado O, Head R, Martins R, Masters CL, Ames D, Villemagne VL. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging*. 2010; 31:1275–1283. [PubMed: 20472326]
 31. Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM. Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. *Neuron*. 2004; 43:321–332. [PubMed: 15294141]
 32. Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. *Arch Neurol*. 2011; 68:1062–1064. [PubMed: 21482918]
 33. Gomez-Isla T, Price JL, McKeel DW Jr, Morris JC, Growdon JH, Hyman BT. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J Neurosci*. 1996; 16:4491–4500. [PubMed: 8699259]

34. Sperling RA, Jack CR Jr, Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, Brashear HR, Grundman M, Siemers ER, Feldman HH, Schindler RJ. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement*. 2011; 7:367–385. [PubMed: 21784348]
35. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:280–292. [PubMed: 21514248]
36. Fox NC, Black RS, Gilman S, Rossor MN, Griffith SG, Jenkins L, Koller M. Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. *Neurology*. 2005; 64:1563–1572. [PubMed: 15883317]

Fig. 1.

Optimal stage for intervention? Shown is a scheme of the proposed stages of AD with potential prevention and treatment targets. We have depicted the hypothetical dynamic trajectories of currently available biomarkers of the AD pathophysiological process over the clinical course of the disease by plotting biomarker measurements (from normal to abnormal ranges) on the y-axis versus the defined clinical stages of AD on the x-axis. Primary prevention trials would occur in individuals who do not yet have evidence of AD pathology, whereas secondary prevention trials would occur in individuals who have evidence of early pathology on biomarkers of AD but do not yet have clinically evident symptoms, meeting criteria for MCI.

Table 1

Current and future targets of disease modifying therapies for Alzheimer's disease

1	Decrease A β production
	– β -secretase inhibition
	– γ -secretase inhibition or modulation
	– α -secretase enhancement
2	Decrease A β aggregation
	– Decrease metal ion mediated fibrilization
	– Decrease oligomer formation via reduction of A β monomer
	– Decrease plaques via blocking β -pleated sheet formation
3	Increase A β degradation
	– Insulin-degrading enzyme (IDE) activation
	– Neprilysin activation
4	Increase A β clearance
	– “Active” vaccination with truncated A β peptide
	– Passive immunization with monoclonal antibody against A β epitope
	– Passive immunization with antibody against specific conformational forms of A β (e.g. oligomers, protofibrils, or plaque)
5	Decrease tau and neurofibrillary tangle formation
	– Prevent tau hyperphosphorylation
	– Decrease tau aggregation
	– Stabilize microtubules
	– Active and passive immunization against tau
6	Neuroprotection and/or Neuroregeneration
	– Anti-oxidant and other agents to preserve metabolic and/or mitochondrial function
	– Anti-apoptotic agents
	– Decrease inflammatory damage
	– Nerve growth factor enhancement
	– Stem-cell replacement