PERSPECTIVE

Preventing Alzheimer’s Disease

Dennis J. Selkoe

Despite intensive laboratory and clinical research over three decades, an effective treatment to delay the onset and progression of Alzheimer’s disease is not at hand. Recent clinical trial failures strongly suggest that we must treat the disease earlier than in its mild to moderate stages, and major progress in validating presymptomatic biomarkers now makes secondary prevention trials possible. We will learn more about the natural history of the disease and any partial therapeutic responses from detailed analyses of recent trial results. This process will likely position the field for success, but only with much greater investment in all aspects of Alzheimer research and with careful design of future trials.

Few diagnoses in modern medicine evoke deeper apprehension in patient and family than Alzheimer’s disease (AD). The implications of having cardiovascular disease, cancer, or metabolic disease are ominous, and surveys suggest that people particularly fear developing AD. This is so because Alzheimer’s robs us of our most human qualities—reasoning, memory, abstraction, language, emotional control—and because a disease-modifying treatment remains beyond reach. This enormously common neurodegenerative disorder affects more than 5 million Americans and well over 35 million worldwide, numbers expected to grow dramatically as the population ages and competing causes of death in late life continue to recede (1). The projected rate of rise is even greater in the developing world than in the high-income countries (2) (Fig. 1).

As with other slowly progressive diseases, preventing AD depends on understanding early steps in its pathogenesis. A worldwide research effort during the past quarter century has yielded an increasingly detailed picture of the cytopathological, biochemical, and genetic underpinnings of the disease, including in its presymptomatic phase, and the parallel development of biomarker and neuroimaging modalities [reviewed in (3, 4)]. The classical lesions that Alois Alzheimer called attention to a century ago—extracellular amyloid plaques and intraneuronal neurofibrillary tangles—were shown in the mid-1980s to be composed, respectively, of the 42-amino acid β-amyloid protein (Aβ42) and the microtubule-associated protein tau. By the mid-1990s, decreased Aβ42 levels and increased tau levels in cerebrospinal fluid (CSF) were associated with a clinical diagnosis of AD (5). Soon, lowered CSF Aβ42 levels were documented in older people who appeared to have very early AD (sometimes referred to as mild cognitive impairment—amnestic type) or were still cognitively normal (6), with the rise in CSF tau levels generally following the Aβ42 decline (4). In the realm of neuroimaging, progressive hippocampal and cortical atrophy were measured with increasing precision before and during the clinical phase of AD, and this brain shrinkage was found to be accompanied by decreased cerebral metabolism on fluorodeoxyglucose positron emission tomography (FDG-PET). By 2004, the synthesis of a blood brain barrier penetrant, radiolabeled analog of the amyloid-binding dye thioflavin T [Pittsburgh compound B (PbB)], enabled researchers to image fibrillar amyloid deposits in vivo by PET (7). Taken together, these quantifiable markers of the evolving disease process in living human participants, now widely replicated in multiple studies (8), provide a critical resource for validating preventative and therapeutic agents in AD.

Pinpointing a Predisposition to AD

A small fraction (<1%) of all AD cases arises during middle age because of inherited missense mutations in one of three genes: APP, PSEN1, or PSEN2. The APP gene codes for the 695-amino-acid-long β-amyloid precursor protein (APP), which has salutary functions during brain development and in various biological processes in adulthood (9). All AD-causing mutations in APP alter amino acids within or immediately flanking its small ~42-residue Aβ region. The PSEN1 and PSEN2 genes code for two homologous (and redundant) intramembrane aspartyl proteases, presenilin 1 and presenilin 2 (10, 11). Therefore, all of these AD-causing mutations directly affect the biochemical reaction that generates Aβ42 and related peptides throughout life, by altering the substrate (APP) or the protease that cleaves this substrate (i.e., presenilin, the catalytic component of γ-secretase). The full penetrance of the mutations for early-onset, autosomal dominant AD and the fact that they result in a neuropathological, biochemical, and clinical phenotype largely indistinguishable from typical, late-onset (“sporadic”) AD provide strong genetic evidence for the amyloid or Aβ hypothesis, which posits that AD arises in substantial part from a chronic imbalance between Aβ production and Aβ clearance in the brain. Numerous families carrying APP, PSEN1, or PSEN2 mutations have been studied collectively to determine the time course of fluid biomarker changes, neuroimaging changes, and clinical changes before the expected onset of AD symptoms, which is based on the age of symptom onset in a parent with the same mutation.

Initial analyses of a familial AD cohort [the Dominantly Inherited Alzheimer Network (DIAN)] suggest that Aβ42 levels in CSF begin to decline as early as 25 years before expected symptom onset (12). This is followed by the appearance of fibrillar amyloid deposits in the brain (as detected by Pib-PET), increased levels of tau in CSF, and progressive brain atrophy roughly 15 years before expected symptom onset (12). Cerebral hypometabolism and subtly impaired episodic verbal memory seem to begin some 10 years or so before expected symptoms (12). If this time course is generally similar to that of sporadic AD, and there is evidence from cross-sectional studies that it may be (4), then humans destined to develop AD have detectable biochemical and histopathological abnormalities two decades or more before overt clinical symptoms (Fig. 2). Two key lessons that emerge from such studies of presymptomatic AD are that (i) profound brain alterations occur well before the dementia can be diagnosed (13) and (ii) therapeutic interventions directed only at the mild-to-moderate clinical stage may be too late to ameliorate symptoms. The latter conclusion is supported by recent phase 3 trials of certain Aβ-clearing monoclonal antibodies (e.g., bapineuzumab) that failed to significantly slow clinical decline over 18 months, even though such antibodies are capable of preventing...
further rises in amyloid burden (14, 15) and lowering CSF phospho-tau levels, a key biomarker of AD-type neuronal degeneration (16).

**Moving Toward Prevention Trials**

Although antibodies against Aβ (anti-Aβ) that enhance clearance of the peptide and other Aβ-lowering agents, such as inhibitors of the β- and γ-secretase enzymes that generate Aβ, may still be shown to provide benefit in mildly symptomatic AD if given to patients for longer periods, the AD field has moved toward a consensus that secondary prevention (diagnosing and treating the disease before overt symptoms) is more likely to slow the pathogenic process (17–19). Such trials might be designed in the following way. Presymptomatic participants who bear determinantal mutations in APP, PSEN1, or PSEN2 (i.e., autsomal dominant AD) could undergo treatment with an Aβ-lowering or -neutralizing agent beginning 2 to 5 years or more before the ex-

---

**Fig. 2.** Aligning potential disease-modifying agents for AD with the course of the disease. Red boxes indicate the sequence of steps in the discovery of compounds or biologics as investigational new drugs (INDs) for AD. Blue boxes, speculative stages in the long presymptomatic and symptomatic phases of AD in a hypothetical individual who undergoes Aβ buildup for one of several possible reasons (e.g., a presenilin or APP mutation, ApoE4 inheritance, increased β-secretase activity, etc.) and develops very early symptoms by around age 70. Green boxes, clinical trial categories dependent on the stage of AD. Red X, trials in moderate AD not recommended. Yellow X, trials in mild AD recommended with caution. [Figure adapted from (35).]
pected age of onset of frank symptoms. In such trials, enrollees would have low CSF Aβ42 levels as well as brain amyloid deposits (detected by PET imaging) that exceed normal thresholds, ensuring that they can potentially respond to an anti-Aβ treatment. Participants who do not yet have elevated CSF levels of tau or phosphorylated tau at trial entry could be compared with participants who already have these markers of tangle-associated neurodegeneration. Regarding outcomes, the treatment’s capacity to delay the aforementioned biomarker changes [amyloid-PET and FDG-PET abnormalities; cerebral atrophy by volumetric magnetic resonance imaging (MRI); rising CSF levels of tau and phosphorylated tau] could be assessed yearly to ascertain the earliest point of deflection from the pathogenic trajectory of placebo-treated mutation carriers. Salutary movements of biomarkers would be expected to be seen first, but these might be accompanied by less decline on challenging cognitive tests that are sensitive to the cardinal manifestations of very early clinical AD (e.g., episodic memory loss and word learning and retrieval deficits) rather than more global cognitive tests [e.g., Alzheimer’s Disease Assessment Scale–cognitive (ADAS-cog), miniminal state examination (MMSE)] that have less sensitivity to detect early progression. Combined assessment of AD biomarker status and episodic memory should indicate whether the agent in question can slow disease progression over a 3- to 5-year interval. An academic consortium sponsored by the U.S. National Institutes of Health (NIH) and the biotechnology company Genentech has recently been approved to carry out such a secondary prevention trial with an anti-Aβ (crenezumab) in ~300 presymptomatic members of a large Colombian pedigree with the presenilin 1 Glu280Val mutation (DIAN sites and certain pharmaceutical companies).

In the future, additional CSF analytes (e.g., other cytokines, certain lipids, metal ions, etc.) could provide a more sophisticated picture of the AD biochemical phenotype in vivo and also be used as biomarkers of progression.

The notion that lumbar puncture is uncomfortable and generally unacceptable to patients is badly out of date. Some investigators in Europe have been collecting CSF samples from participants with symptomatic and presymptomatic dementia for many years, and clinicians in the United States need to catch up. The Alzheimer’s Disease Neuroimaging Imitative (ADNI; sponsored by the NIH and numerous biopharmaceutical companies) and some individual AD research centers have documented how feasible and informative routine CSF analysis can be [e.g., (27, 28)]. Patients and their families are usually amenable to lumbar puncture once they are informed of how important it is for accurate diagnosis and for assessment of trial outcomes, and the procedure can be quickly and safely performed in an outpatient setting (26). Ideally, each academic center or practice participating in AD trials should designate one or two highly experienced physicians to perform all the lumbar punctures, as is done for other minimally invasive diagnostic procedures such as arthroscopy. Although the advent of PET amyloid imaging is a great boon to the presymptomatic diagnosis of AD, a low CSF level of Aβ42 is an equally if not more sensitive biomarker indicating that cerebral Aβ deposition is underway (29), and this information can be acquired at less expense than a PET scan.

Such considerations underscore the reality that we cannot validate efficacious disease-modifying agents in AD without strong reliance on biomarkers. The AD field often discusses the compelling example of blood lipid profiling in coronary artery disease (CAD), which led to regulatory approval of the first statin years before these low-density lipoprotein (LDL)-cholesterol–lowering drugs were unequivocally proven to prevent heart attacks (29). This achievement occurred because elevated cholesterol levels and abnormal lipoprotein profiles in blood had been tightly linked to the risk of progressive CAD by many epidemiological and mechanistic studies (30). The AD field is now approaching an analogous benchmark, with numerous CSF and neuroimaging studies consistently validating early changes in CSF Aβ42 and tau levels and cerebral amyloid deposition as indicative of a high risk of developing disease (8). It took years of clinical use of statins to be certain that therapeutically lowering LDL-cholesterol actually helped prevent morbidity and mortality in CAD (i.e., prove the cholesterol hypothesis) (29), and yet statin treatment was approved and rapidly expanded before that. Because neuropathological, genetic, mechanistic, biomarker, and even therapeutic research all support an early pathogenic role of Aβ42, the AD field needs to follow suit. Although sensitive memory tests should always accompany biomarker assays in secondary prevention trials, rigorous and statistically significant outcomes on brain and CSF Aβ and tau should be considered for regulatory approval as long as an amyloid-lowering agent is deemed safe. Only with more widespread and prolonged use of a well-tolerated agent that hits AD biomarker endpoints can we ultimately determine whether the agent is efficacious on quality-of-life outcomes. Surveys indicate that many patients and their families are willing to undergo experimental testing of preventatives or early treatments, given the current absence of an approved disease-modifying therapeutic for this terrible, fatal disease. Approval of a safe agent that was designed on the basis of our current best understanding of AD mechanism should be considered.
on biomarker grounds alone, as has sometimes occurred in other chronic, life-threatening diseases.

Beyond Aβ

Why have agents targeting Aβ received so much therapeutic attention in AD? The principal reason is the wealth of evidence from many independent investigators worldwide supporting an early role for Aβ dyshomoeostasis in AD pathogenesis. Nonetheless, there remain appropriate concerns about Aβ as a cause and as a worthy therapeutic target in AD. Some of the considerable controversy that has swirled around this topic may represent misunderstandings of data and goals. I will describe just two key examples. First, there remains debate about whether Aβ accumulation is a cause or an effect of AD. Almost certainly, the answer is both. When APP or presenilins are mutant, Aβ overproduction appears to be the earliest identifiable molecular event associated with the development of AD. But in the vast majority of cases, an imbalance between Aβ production and clearance, which occurs in 100% of patients as we define AD, is caused by other upstream events, most currently unknown. One very important known cause is inheritance of one or two e4 alleles of the apolipoprotein E gene (31). Such cases were once part of the broad swath of sporadic AD, but we now recognize ApoE4 as the single greatest risk factor for the disease besides age. Compelling evidence indicates that the ApoE4 protein decreases cellular clearance of Aβ and enhances the stability of extracellular Aβ aggregates in brain (32), but evidence for additional, non-Aβ-mediated effects, including on tau, is also accruing (33). Even though Aβ cannot be said to be causative in ApoE4 carriers (who may number at least half of AD cases), an agent that chronically reduces Aβ production (e.g., a β-secretase inhibitor or a γ-secretase modulator) or enhances its clearance (e.g., a passively administered Aβ antibody or an active Aβ vaccine) should be efficacious. In short, Aβ is both cause and effect in AD.

A second misunderstanding is the notion that therapies lowering Aβ could be dangerous because they would decrease the peptide’s normal functions. Even years before symptomatic AD, brain levels of Aβ are very substantially increased, and no currently contemplated therapeutic would be expected to reduce them to subphysiological levels, just as therapeutic statin doses do not cause serum cholesterol to fall to dangerously low levels. Whether the Aβ fragment of APP acquired a biologically important function during evolution distinct from those of other proteolytic fragments of the precursor is under intensive study. For example, a recent report found that Aβ40 and Aβ42 peptides can favorably modify peripheral lymphoid and myeloid cell function to mitigate against experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis (34). But lowering the excessive brain levels of soluble Aβ peptides in AD to subphysiological levels is not contemplated and would be difficult to achieve.

These and other specific controversies surrounding the Aβ hypothesis have been discussed (35) and are widely viewed as not precluding further human research on Aβ-lowering strategies. At the same time, it is crucial to expand more preclinical and clinical research effort on non-Aβ strategies—for example, lowering excess levels of tau proteins or down-regulating inflammatory cells both centrally and peripherally. Unfortunately, these approaches are well behind therapeutic development in the Aβ arena. We must substantially increase research on these alternative targets while also accelerating our judicious testing of Aβ-directed agents in presymptomatic or very early AD. Current research funding for AD is not nearly sufficient; it still represents a modest portion of the dollars our field needs to study AD comprehensively, and it is a very small fraction (<1%) of the enormous costs our society bears each year to provide care to AD patients.

Reducing AD Risk Without Drugs

Our understanding of environmental factors that modulate one’s risk of developing AD lags behind our knowledge of the contributing genetic factors. Nonetheless, this important topic has been receiving increasing scrutiny. Lifestyle factors that may reduce the risk of dementia in general and AD in particular include physical exercise, cognitive activity and educational attainment, and social engagement. The protective effect of aerobic exercise (36, 37) may derive from enhanced cardiovascular fitness and cerebrovascular health but possibly also from modifying the biology of AD; for example, by lowering Aβ accumulation or decreasing neurotic dystrophy. Lifelong intellectual activity and higher educational levels have been found to lessen the risk of developing AD or to ameliorate its course (38, 39). In mouse models, environmental enrichment, including repeated exposure to novelty, has been shown to decrease amyloid burden and attendant neuroanatomical and behavioral deficits (40, 41). Strong social engagement and lack of isolation in the elderly may contribute to a lower likelihood of developing dementia, including AD, or a slower progression of symptoms (42, 43). Our current state of knowledge suggests that changes in lifestyle are unlikely to be sufficient to stave off the development of AD, particularly if these changes are instituted close to the time of clinical onset. However, it is possible that exposure to beneficial lifestyle factors over many years could delay the onset and progression of the disease. This research area merits rigorous investigation, given the ongoing challenges of validating a safe disease-modifying therapeutic and the high costs that will be incurred with its chronic administration.

Success from Failure

Attempts to treat complex, chronic diseases such as AIDS or certain forms of cancer have been marked by major failures before tangible success emerged. One hopes that this will be the case in AD. The appropriately intensive effort to test potential AD therapeutics earlier and in more carefully designed trials is likely to lead to rigorous scientific evidence of disease modification before long. This evidence may arise principally from biomarker data, although it will likely be accompanied by positive trends on cognitive tests. Despite being enormously disappointing to patients, families, and physicians, the field’s recent clinical trial failures will provide a great deal of concrete information about what may work partially, what does not, and where to go next. As a society, we must invest much more and invest more wisely. We must broaden our therapeutic vision beyond Aβ and also move quickly to trials in very early symptomatic as well as presymptomatic participants. As soon as we see independently replicated evidence of relevant biomarker changes and some cognitive benefit, we should begin to consider even earlier (“primary”) prevention trials for middle-aged participants bearing ApoE4 alleles. Our patients and their families should remind us of Churchill’s exhortation: “...never, never, ever quit!”

References and Notes


MS no: PS1228541/TW/MEDICINE

Acknowledgments: The author serves on the board of directors of, and is a paid consultant for, Elan Corporation, plc, a biotechnology company that is developing therapies for neurodegenerative diseases, including AD.

10.1126/science.1228541