100 Years and Counting: Prospects for Defeating Alzheimer's Disease

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Abstract

This week marks a century since the first description of Alzheimer's disease (AD). Despite approval of several drugs for AD, the disease continues to rob millions of their memories and their lives. Fortunately, many new therapies directly targeting the mechanisms underlying AD are now in the pipeline. Among the investigative AD therapies in clinical trials are several strategies to block pathogenic amyloid-β peptides and to rescue vulnerable neurons from degeneration. Complementary but less mature strategies aim to prevent the copathogenic effects of apolipoprotein E and the microtubule-associated protein tau. New insights into selective neuronal vulnerability and the link between aging and AD may provide additional entry points for therapeutic interventions. The predicted increase in AD cases over the next few decades makes the development of better treatments a matter of utmost importance and urgency.

It used to be said that neurologic diseases were easy to diagnose but impossible to treat. Today, effective treatments are available for many neurologic conditions, but for the 4.6 million new patients worldwide who will be affected by AD this year (1), the old mantra still rings too true. Although multiple drugs have now been approved, their expected benefits are modest. One hundred years after the discovery of AD, the lack of treatments with a major impact might be discouraging. Fortunately, basic research is identifying many of the pathways that contribute to this devastating disease (Fig. 1), providing unprecedented opportunities for the development of new treatments aimed at the root causes of AD. Here, we review several of these efforts and consider both shorter- and longer-term prospects for effectively treating AD.

Current Standard of Care

Five drugs are approved in the United States for the treatment of AD (2, 3), although tacrine is now rarely used because of hepatotoxicity (Table 1). Cholinesterase inhibitors are designed to combat impairment of cholinergic neurons by slowing degradation of acetylcholine after its release at synapses. Memantine prevents overstimulation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors, which may contribute to the pathogenesis of AD and other neurodegenerative conditions by causing excito-toxicity (4). In clinical trials, both cholinesterase inhibitors and memantine have shown beneficial but modest effects on cognitive test scores, behavioral measures, and functional outcomes (5–9). However, because the benefits of cholinesterase inhibitors are small and may be seen in only a subset of patients, their cost effectiveness has been questioned (10). Because memantine is beneficial in patients already taking cholinesterase inhibitors and may even reduce their side effects, the two are often used together (9). Many AD patients also receive antipsychotics or anti-depressants to manage neuropsychiatric and behavioral symptoms or take over-the-

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counter preparations whose therapeutic value is uncertain, including ginkgo biloba and vitamins C and E (2, 11–14).

In the Pipeline: Targeting Aβ

The marginal benefits of current therapies emphasize the need for more potent AD drugs. Several new compounds are now being tested for safety (phase I and IIA) and efficacy (phase IIB and III) in clinical trials (Table 2) (15). To date, emphasis has been on strategies to reduce the pathogenicity of amyloid-β (Aβ) peptides (16), widely believed to play a key role in AD.

Reducing Aβ production is one goal. Aβ is generated from the amyloid precursor protein, APP, via sequential cleavage by β- and γ-secretase (Fig. 2). γ-Secretase inhibitors have reached clinical trials, but published results are limited. One compound, LY450139, was well tolerated and reduced the amount of Aβ in the plasma, but not in the cerebrospinal fluid (CSF) (17). The potential for dose escalation is limited, because γ-secretase also cleaves other substrates, including Notch, and nonselective γ-secretase inhibitors have deleterious effects on embryogenesis in zebrafish and on lymphoid and gastrointestinal tissues in mammals (18, 19).

Thus, several approaches are being pursued to design next-generation γ-secretase drugs that selectively reduce APP cleavage (Fig. 2). As opposed to the standard strategy of inhibiting proteases by blocking their active sites, one approach targets the substrate-docking site of γ-secretase to selectively interfere with APP binding (20). Another idea capitalizes on the observation that γ-secretase has an adenosine triphosphate (ATP)–binding site that selectively modulates APP processing (21). Blocking this site inhibits APP, but not Notch, cleavage (22). Yet another approach is to modulate, rather than inhibit, γ-secretase activity. Besides the γ site, γ-secretase also cleaves at a more C-terminal ε site critical for proper Notch signaling. The TMP21 accessory component of γ-secretase suppresses γ-cleavage without affecting ε-cleavage of APP or Notch, suggesting a means to inhibit Aβ production without Notch-dependent adverse effects (23). Lastly, even at the γ site, APP can be cleaved at different positions, creating 40– or 42–amino acid forms; the $A\beta_{42}$ peptide appears to be the most pathogenic. Certain nonsteroidal anti-inflammatory drugs (NSAIDs) allosterically modulate γ-secretase to favor production of $A\beta_{40}$ over $A\beta_{42}$ (24, 25) and are now in phase III trials.

β-Secretase, whose cleavage of APP precedes that of γ-secretase (Fig. 2), is another prime target to inhibit Aβ production. It has fewer known substrates than γ-secretase and a more benign gene-knockout phenotype in mice (26), suggesting that β-secretase inhibitors may be safer than γ-secretase inhibitors. Genetic elimination of β-secretase prevented memory deficits in human APP transgenic mice (27). For structural reasons, it has been more difficult to design small-molecule inhibitors for β-secretase than for γ-secretase, but this problem appears to be surmountable (26). Other APP-cleaving enzymes might also be good targets. Stimulating α-secretase can reduce Aβ because the enzyme cleaves APP within Aβ (28–30). Preventing caspase cleavage of the APP intracellular domain may also be beneficial (31).

Promoting Aβ clearance by immune mechanisms is another promising approach (32). In a phase II trial, active immunization with $A\beta_{42}$ plus adjuvant appeared to reduce amyloid deposits in some brain regions, improve certain cognitive measures, and ameliorate CSF abnormalities in patients who developed antibodies (about 20% of those in the treatment group). However, the trial was halted because 6% of immunized patients developed meningoencephalitis (32). Because this complication was likely mediated by a T helper 1 (T_H1)–cell response, much effort has been made to circumvent that arm of the immune

response while preserving the beneficial effect of antibodies against Aβ (anti-Aβ) on amyloid removal by microglia and blood-derived macrophages (32).

One approach is passive immunization with anti-Aβ, avoiding the T cell response (33). Although passive immunization resulted in cerebral microhemorrhages in some human APP transgenic mouse lines (34), antibody deglycosylation circumvents this complication (35). An ongoing phase IIA trial of passive immunization has progressed to an advanced stage without interruptions due to adverse events.

Active immunization with Aβ may still be useful too. In APP transgenic mice, immunization with the $Aβ_{1-15}$ fragment (36) or with Aβ coupled to carrier protein (32) led to amyloid clearance without activating the undesired T cell response. Delivering Aβ through the nasal mucosa may also avoid adverse T cell effects seen with intramuscular injections (37). However, given the complications of the original immunization trial, the utmost caution is required in extrapolating these results to humans. Interestingly, the immune-modulatory polypeptide glatiramer effectively cleared amyloid deposits in APP mice independently of anti-Aβ (38). This drug is already used to treat multiple sclerosis and will likely soon be tested in AD patients.

Lastly, certain small molecules disrupt Aβ aggregation. Although published data are limited, such compounds show promise in animal models (39, 40) and are in phase III clinical trials.

Clinical Trials Beyond Aβ

Not all current clinical trials are aimed at Aβ. Because depletion of nerve growth factor (NGF) may contribute to loss of cholinergic neurons in AD, boosting NGF has been pursued using several strategies (41). In the boldest procedure, fibroblasts are isolated from AD patients, transduced with an NGF-encoding viral vector, and implanted stereotactically into the forebrains of patients (42). Although only eight subjects were tested in the phase I trial, the procedure was reasonably well tolerated when carried out under full anesthesia and may have improved cognitive performance and cerebral perfusion.

Several "off-the-shelf" drugs are also being tested for efficacy in AD. For example, NSAIDs (43) and cholesterol-lowering statins (44) were associated with decreased risk of developing AD in retrospective series. Prospective trials, though, have been mostly disappointing. Some interpret the negative prospective trials as too little too late and argue for retesting in prevention trials. Others suspect that the negative trials reflect the weaknesses of retrospective data, e.g., that other factors distinguish NSAID users from non-users and may be responsible for the differential AD risk. Because prevention trials are generally even larger and more expensive than treatment trials, this issue has major implications for resource allocation in the field, and debate remains about whether funds would be better devoted to supporting more basic research and developing more effective drugs.

The pleiotropic actions of NSAIDs and statins complicate matters further. For example, some NSAIDs have anti-Aβ as well as anti-inflammatory properties (43). Notably, most negative prospective NSAID trials tested only selective cyclooxygenase 2 (COX-2) inhibitors (to reduce gastrointestinal side effects), but these drugs lack the anti-Aβ effects of other NSAIDs and may even increase Aβ production (43, 45). Whether optimized NSAIDs that safely combine anti-Aβ and anti-inflammatory activities will be more efficacious remains to be determined.

Lastly, several drugs have been developed to ameliorate AD-related abnormalities by modulating various neurotransmitter receptors (Table 2) (15). Some provide primarily

symptomatic benefits and others may directly target AD pathogenesis, but their effectiveness in AD remains unclear (15).

Neglected Opportunities

The apolipoprotein E (*APOE*) ε4 allele has emerged as the major genetic risk factor for AD, whereas individuals with ε2/ε2 or ε3/ε2 genotypes rarely develop the disease (46, 47). Nature seems to be suggesting an important avenue toward treating this disease, but specific strategies had been lacking. However, promising new approaches to counteracting the adverse effects of apoE4 or leveraging the beneficial effects of apoE2 or apoE3 are beginning to emerge from basic research (48, 49).

The two domains of apoE interact more closely with each other in apoE4 than in the other apoE isoforms, which may account for many of apoE4's adverse effects (48, 49). Compounds that disrupt domain interaction, inducing apoE4 to adopt a more beneficial structure and function, are being developed. In addition, selective pathogenic cleavage of apoE4 yields a truncated apoE that may impair mitochondrial energy production and disrupt the cytoskeleton (Fig. 1). When identified, the putative apoE-cleaving enzyme may be an attractive drug target (49). Complementary efforts exploit the differential effects of apoE isoforms on the formation and clearance of amyloid deposits (50–52).

Another molecule that may have been inadvertently overshadowed by Aβ is the microtubule-associated protein tau, the main constituent of neurofibrillary tangles. Tau undergoes many AD-related posttranslational modifications (53). Tau phosphorylation increases dramatically in AD (54), suggesting tau kinase inhibitors as an AD treatment. Lithium, which inhibits tau phosphorylation with beneficial effects in animal models, is in clinical trials. However, potential redundancy between the many kinases that phosphorylate tau and uncertainty about which phosphorylation events are truly pathogenic raise challenging issues in the design of tau kinase inhibitors. Other approaches to tau include blocking its aggregation, either directly (55) or by inhibiting its proteolysis (56). Because hyperphosphorylated tau tends to dissociate from microtubules, reducing their stability, microtubule-stabilizing drugs represent an alternative approach (57).

Another approach to apoE, tau, and even APP may be reducing their overall amounts without targeting particular posttranslational modifications; because mild (~20%) overexpression of APP or tau increases AD risk (58, 59), reducing their overall concentrations by a similar magnitude might decrease AD risk. Even complete ablation of these proteins in knockout mice is rather well tolerated (60–62). Small molecules that suppress APP or tau concentrations have already been identified (63, 64). Proof-of-principle studies are needed to determine whether such strategies will prevent cognitive impairment in animal models of AD.

Unresolved Questions with Therapeutic Implications

Basic research has paved the way to new drugs in clinical trials, but several fundamental questions about AD remain. Resolving these issues could usher in the next generation of therapeutics.

The selective vulnerability of specific neuronal populations to AD is one such issue. It is unclear whether this vulnerability relates to cell-autonomous structural, biochemical, or electro-physiological properties; to interactions with glial cells; or to the extracellular milieu in specific brain regions. Recent studies have added yet another possibility to the list: differences in neuronal activities within distinct neural networks.

There is striking overlap between the anatomic regions most affected by AD and the "default-mode" network, active when the mind is focused on nothing in particular (65, 66). Because neuronal activity increases the production and release of Aβ, excessive activity in the default-mode network might make it vulnerable to AD (66–68). This pathogenic interaction may also explain, at least in part, the beneficial effects of mental activity and environmental enrichment (69, 70), which should decrease activity and, thus, Aβ in this network. Rapid fluctuations of cognitive function that cannot be explained by neuronal loss raise additional possibilities for the therapeutic modulation of network activities (71).

Another important question relates to the link between aging and neuro-degenerative disorders. Can it be manipulated to prevent or delay AD? A cadre of peptidases is essential to clear Aβ from the brain (72–74), and their activity appears to decline with age, possibly contributing to AD (74–76). Boosting Aβ-degrading enzymes, such as neprilysin (77, 78), endothelin-converting enzyme (79), or cathepsin B (74), protects transgenic mice from Aβ, highlighting their therapeutic potential. Because it is difficult to pharmacologically activate these enzymes, the best way to leverage their Aβ-degrading activities may be through druggable factors that regulate them naturally (79, 80).

Oxidative stress is a widely explored link between aging and neurodegenerative diseases (4, 14). Given the ample evidence for oxidative stress in AD, it is surprising that trials of antioxidants, such as vitamins C and E, have yielded mostly disappointing results (12, 14). Have the right compounds not yet been tested? Trials of other antioxidants such as coenzyme Q10 and curcumin are ongoing. Or might it be better to focus on activating intrinsic defense systems, for example, through caloric restriction, which reduces oxidative stress, delays aging, and may lower AD risk (81, 82)?

Stem cells are often touted as a potential AD treatment. However, even beyond the much-discussed ethical and political hurdles, there are important scientific questions about potential use of stem cells for AD (83–85). For example, AD affects different types of neurons in multiple brain regions; how many must be replaced, and can stem cells differentiate into all the necessary populations? Would stem cell grafts integrate both structurally and functionally into vulnerable neuronal networks? Or might these grafts provide benefits through integration-independent effects, such as neurotrophin release? In either case, will the aged brain support their therapeutic activities? Moreover, will their treatment capacity be limited in the milieu of Aβ, apoE4, tau, and inflammatory mediators found in the AD brain? Definitive answers to these questions are needed but may not become available for many years.

Lastly, when exactly does AD begin, and how early will one have to intervene with pathogenic mechanisms to prevent its clinical manifestations? More and more emphasis is being placed on early detection, based on the reasonable assumption that AD will be easier to prevent than reverse. Whether earlier really is better will depend, in large part, on the safety and side effect profiles of emerging AD treatments, as highlighted by ongoing debates about the best timing for treatments of other chronic conditions, such as HIV infection and Parkinson's disease (86, 87).

Conclusions

When the secretases that produce Aβ were first identified in the late 1990s, some people felt that the writing was on the wall for AD: A little effort on protease inhibitor development and the end was near. Today, most are substantially more circumspect, and there seems to be consensus that multiple drugs will be required. For one, the field now recognizes the important pathogenic roles of molecules beyond Aβ. Indeed, it seems likely that, for

example, an AD patient with a genetic mutation causing Aβ overproduction and an AD patient with two *APOE* ε4 alleles plus a history of head trauma might benefit from different regimens, one focused on lowering Aβ and the other including apoE-targeting drugs and neuroprotectants.

The need for drugs with different modes of action and for individualized regimens creates imposing challenges. Clinical trials must carefully consider their inclusion and exclusion criteria, and subgroup analysis becomes critical. Better synergy between industry and academia is required to speed the transition from target identification to drug development. Funding must increase to reduce the mismatch between the rapidly growing economic threat from AD and the limited resources available to fight it.

Notwithstanding these challenges, there is good reason for optimism. With the many exciting prospects now in the pipeline and the steady flow of insights into disease pathogenesis from basic laboratories, the arsenal of clinicians fighting AD should be more fully stocked at the next major anniversary of Alzheimer's discovery.

Acknowledgments

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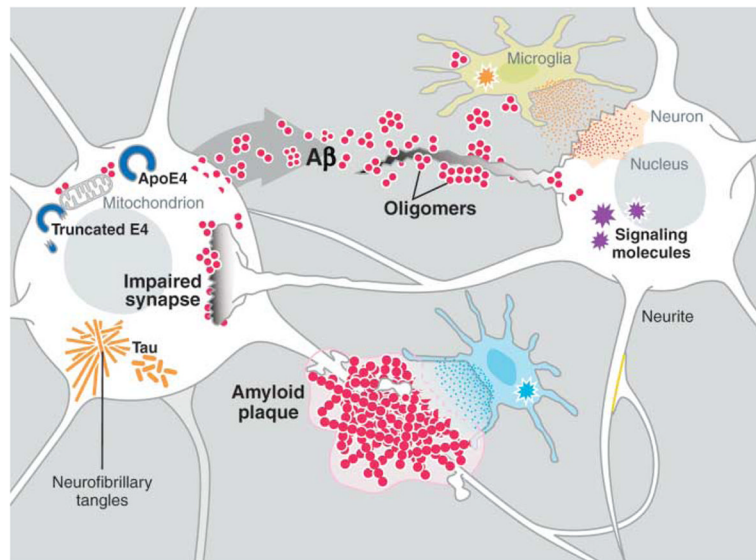90. Alzheimer Research Forum. www.alzforum.org/dis/tre/drc/

Fig. 1.
Molecular and cellular processes presumed to participate in AD pathogenesis. Aβ peptides produced by neurons and other brain cells aggregate into a variety of assemblies, some of which impair synapses and neuronal dendrites, either directly or through the engagement of glial loops. Build-up of pathogenic Aβ assemblies could result from increased production or aggregation or from deficient clearance mechanisms. ApoE4 and tau promote Aβ-induced neuronal injury and also have independent adverse effects. Microglia could be beneficial or harmful, depending on which of their signaling cascades and functions are engaged. This multifactorial scenario leads to progressive disintegration of neural circuits, isolation and loss of neurons, network failure, and neurological decline.
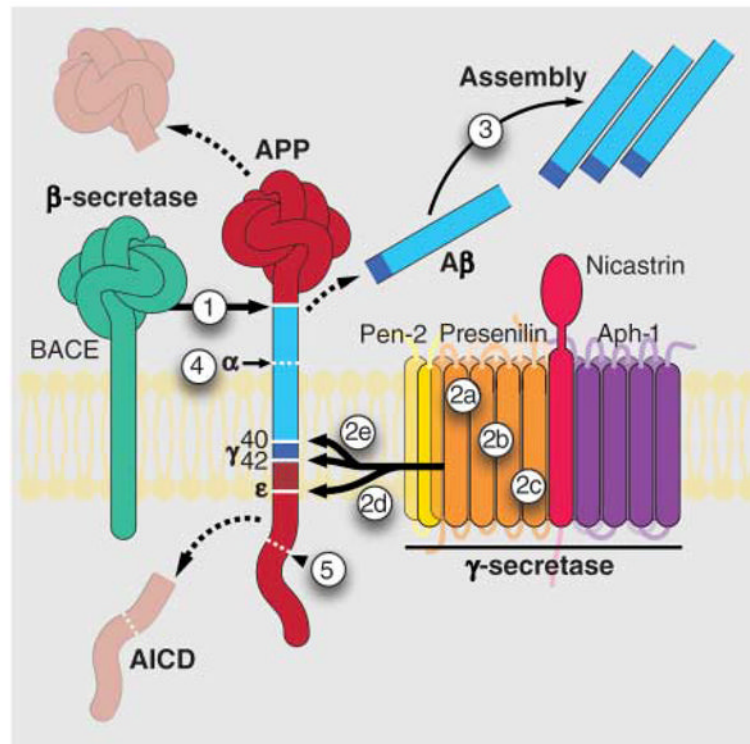
Fig. 2.
Drug targets involved in Aβ production and assembly. Aβ production depends on sequential proteolytic cleavage of APP by β-secretase (marked 1), also known as β-site APP-cleaving enzyme 1 (BACE1), and the multiprotein γ-secretase complex (2) (88). γ-Secretase targets include the enzyme's active site, substrate docking site, and ATP-binding site (2a to 2c) and its predilection for γ-versus ε-cleavage (2d) or for generating $A\beta_{42}$ versus $A\beta_{40}$ (2e). The pathogenicity of released Aβ peptides depends on self-assembly (3). APP cleavage by α-secretases (ADAM family metalloproteases) prevents Aβ production (4). Caspase cleavage of the APP intra-cellular domain (AICD) generates a C31 fragment (5) that may participate in Aβ-induced toxicity or act independently.

Table 1

Food and Drug Administration–approved treatments for AD.

Drug	Approved for
Cholinesterase inhibitors	
Donepezil	Mild to moderate AD
Galantamine	Mild to moderate AD
Rivastigmine	Mild to moderate AD
Tacrine	Mild to moderate AD
NMDA receptor antagonist	
Memantine	Moderate to severe AD

Table 2

Selected treatments in clinical trials for AD. For more information on these and other trials, see (15, 89, 90).

Treatment strategies
Phase III
Aβ aggregation inhibitors
Antioxidants
γ-Secretase modulators
NGF mimics
PPARγ agonists
HMG-CoA reductase inhibitors (statins)
Phase II
Ampakines
Calcium channel blockers
GABA receptor antagonists
γ-Secretase inhibitors
Glycogen synthase kinase inhibitors
Intravenous immunoglobulin
Muscarinic receptor agonists
New cholinesterase inhibitors
Nicotinic receptor modulators
Passive Aβ immunization
Phosphodiesterase inhibitors
Serotonin receptor antagonists
Phase I
Active Aβ immunization
NGF gene therapy