

**The bright future of Alzheimer's disease pharmacotherapy****Jimma L. Lenjisa<sup>1\*</sup>, Gizaw D. Satessa<sup>2</sup>, Minyahil A. Woldu<sup>1</sup>**

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**ABSTRACT**

Alzheimer's disease (AD) is the most common cause of progressive dementia in the elderly population leading to progressive disturbances of cognitive functions. It is the disease whose prevalence is rising but with very limited numbers of drugs limiting its progression making more difficult to overcome the evil side of this disease. Currently, there are a number of drugs in pipeline blooming the hope to effectively modify the progression of AD. All of these newer agents are directing toward the biochemical mechanism of AD development including targeting tau protein (e.g. Inhibition of tau kinase), targeting A $\beta$  (e.g.  $\beta$ -Secretase Inhibitors), and therapies involving gene as well as stem cell strategies. Hence in this review, we summarized the pathogenesis of AD on which the discovery of these newer agents based in addition to giving a clear picture on these agents.

**Keywords:** Alzheimer's disease, Secretase inhibitors, Gene therapy, Stem cell therapy

**INTRODUCTION**

Alzheimer's disease (AD) is the most common cause of progressive dementia in the elderly population. It is a chronic neurodegenerative disorder that leads to progressive disturbances of cognitive functions including memory, judgement, decision-making, orientation to physical surroundings and language. It has been estimated that ~5% of the population older than 65 years is affected by Alzheimer's disease. The prevalence doubles approximately every 5 years beyond age 65 and some studies suggest that nearly half of the people aged 85 years and older suffer from this devastating disorder.<sup>1</sup> In the United States, AD is the sixth leading cause of death, with an estimated 5.3 million Americans having AD. By 2050, according to some estimates, 1 of every 85 persons worldwide will be affected by AD. Currently

available treatments for AD provide largely symptomatic relief with only minor effects on the course of the disease.<sup>2</sup>

The ideal therapies for AD should be not only effectively improving the dementia symptoms but also fundamentally reducing the burden of senile plaques and neurofibrillary tangles and thus protect the neurons from degeneration. Currently several drugs and agents that either affect secretory amyloid precursor degradation, or inhibit amyloid peptides aggregation or block hyperphosphorylated tau protein formation are under investigation in preclinical trials. These new approaches are representatives of current therapeutic development for the treatment of AD.<sup>3</sup> Thus; this review aims at giving brief account on potential mechanism based therapy that can help modify the pathology of AD as compared to symptomatic therapy.

## BIOCHEMICAL BASES OF ALZHEIMER'S DISEASE (AD)

The pathological hallmarks of AD are the accumulation of A $\beta$  as neuritic plaques and congophilic angiopathy and the accumulation of abnormally phosphorylated tau in the form of neurofibrillary tangles (NFTs). Missense mutations in amyloid precursor protein (APP) or in presenilin genes [presenilin 1(PS1) and PS2] can cause early-onset, familial forms of AD.<sup>4</sup>

### 1. Amyloid- $\beta$ (A $\beta$ ) accumulation – neuritic plaques

The known genetic forms of AD are caused by mutations in amyloid precursor protein (APP) which is coded on chromosome 21 or the enzymes that are involved in A $\beta$  formation. The pathway for A $\beta$  plaque formation begins with the pathologic processing of APP. This protein is cleaved first by the protease  $\beta$ -secretase (i.e., BACE-1) and subsequently by  $\gamma$ -secretase to form either the benign peptides A $\beta_{38-40}$  or the neurotoxic peptide A $\beta_{42}$ . Under normal circumstances, the vast majority of A $\beta$  (>95%) consists of A $\beta_{38-40}$ . Through unknown mechanisms, genetic and environmental factors may shift this balance toward increased production of toxic A $\beta_{42}$ . Accumulation

and oligomerization of A $\beta_{42}$  results in the formation of amyloid plaques and initiates a cascade of events associated with neuronal and synaptic dysfunction.<sup>5,6</sup> Figure 2 summarizes these facts.

### 2. Hyperphosphorylated tau protein accumulation - Neurofibrillary Tangles (NFTs)

AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. A protein called *tau* stabilizes the microtubules when phosphorylated. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system.<sup>7</sup> *Tau* pathology develops slowly with increasing age in a large percentage of the population, and this may help explain why age is the major risk factor for AD. Therefore, the pathological hyperphosphorylation of tau, which can be visualized by immunochemical methods, is an early event in the development of Alzheimer's disease related neurofibrillary changes.<sup>8,9</sup> This is clearly shown on figure 1.

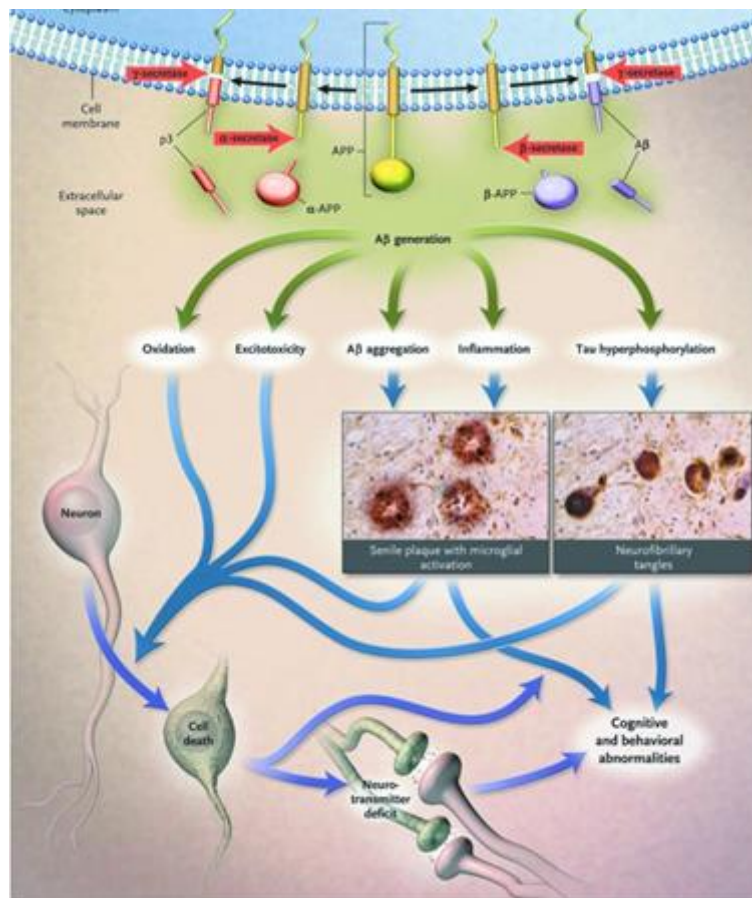
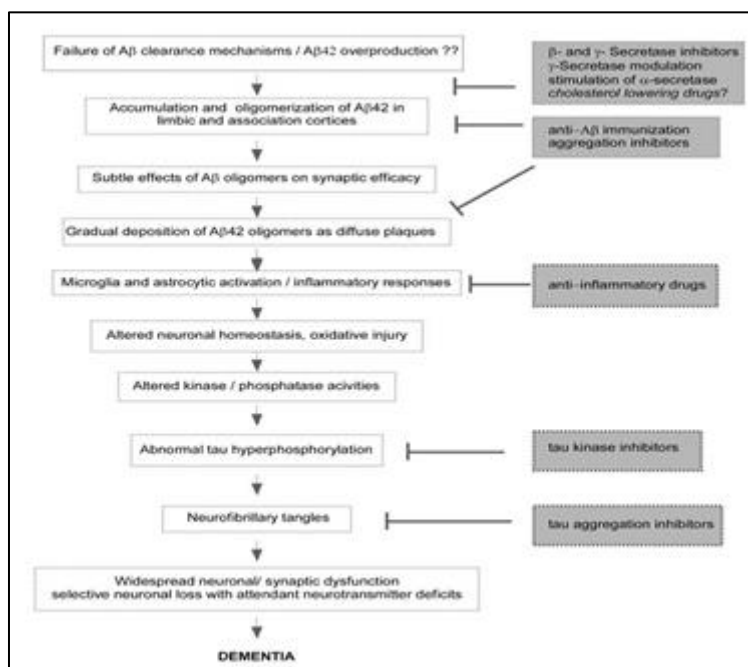


Figure 1: The amyloid hypothesis of Alzheimer's disease.<sup>9</sup>

## TARGET SITES FOR MOST OF THE NOVEL DRUGS IN TREATMENT OF AD

According to the amyloid cascade hypothesis novel therapeutic strategies that lower A $\beta$  levels or prevent the

formation of the presumed neurotoxic oligomeric A $\beta$  species (Figure 2) are predicted to stop or slow down the progression of neurodegeneration and dementia in AD.<sup>1</sup>



**Figure 2: Amyloid cascade hypothesis and selected targets for therapeutic intervention.<sup>3</sup>**

The figure summarizes the presumed sequence of pathological processes that leads to neurodegeneration in AD according to the amyloid cascade hypothesis, and indicates selected potential approaches for therapeutic intervention.

### 1. Therapeutic strategies targeting A $\beta$

#### A. $\beta$ -secretase inhibitors

Although the development of  $\beta$ -secretase inhibitors has lagged behind the development of  $\gamma$ -secretase inhibitors, many believe that  $\beta$ -secretase is likely to be a better therapeutic target.  $\beta$ -secretase is an important biological target for new drug development, but clinical trials have not yet been conducted. While inhibition of  $\beta$ -secretase is not expected to incur the same safety risk as  $\gamma$ -secretase inhibitors, BACE-1 deficiency in genetically engineered mice is associated with impaired learning. In addition, there are significant pharmacokinetic challenges in developing a viable BACE inhibitor. To date, the compounds that effectively inhibit BACE activity are large molecules that do not penetrate the blood-brain barrier.<sup>10,11</sup>

Nevertheless, inhibition of  $\beta$ -secretase is a promising strategy. This therapeutic potential was demonstrated by the findings that BACE-1 knockout mice develop normally, and appear to have completely abolished the production of A $\beta$ , suggesting that BACE-1 is the principal  $\beta$ -secretase in neurons. Such inhibition does not preclude normal processing of APP by the nonamyloidogenic major pathway, and is the first step in the amyloidogenic cascade. Specific BACE-1 inhibitors should therefore have therapeutic potential to slow or halt the progression of this debilitating and ultimately fatal disease, and a number of preclinical candidates are about to enter clinical trials.<sup>12,13</sup>

#### B. $\gamma$ -secretase inhibitors

Identification of the protein responsible for  $\gamma$ -secretase activity, the enzyme that cleaves APP within the membrane, has been very challenging. Much evidence indicates that the catalytic activity resides in presenilins (PS1/PS2), proteins with multiple transmembrane domains, as mutagenesis of 2 aspartates in PS1 eliminated  $\gamma$ -secretase activity.<sup>14</sup>

The  $\gamma$ -secretase activity is associated with a complex of integral membrane proteins that includes, at least, a novel

aspartyl protease, presumably PS, and nicastrin, a protein with a single transmembrane domain. Use of difluoroketone-based compounds as  $\gamma$ -secretase inhibitors has provided insights into the proteolytic activity and suggested such inhibition might be a useful therapeutic strategy. Some compounds are currently in phase I clinical trials.<sup>15</sup>

More progress has been made in developing  $\gamma$ -secretase inhibitors, because high-throughput screens carried out in the pharmaceutical industry have identified numerous  $\gamma$ -secretase inhibitors. Multiple classes of potent  $\gamma$ -secretase inhibitors have now been described, and several of these have been shown to target both PS1 and PS2.<sup>16</sup> Moreover, treatment of mice with a  $\gamma$ -secretase inhibitor reduces A $\beta$  levels in the brain and attenuates A $\beta$  deposition.<sup>17</sup> Nevertheless, target-mediated toxicity caused by interference with  $\gamma$ -secretase is a great concern.<sup>18,19</sup> To tackle this challenge, an attempt is being made in identifying potential targets and highly specific  $\gamma$ -secretase inhibitors that may be translated into the development of efficacious and safe treatments.<sup>20,21</sup>

### C. $\alpha$ -secretase activators

The  $\alpha$ -secretase is a member of a disintegrin and metalloprotease (ADAM) family. The initial APP processing involves the cleavage of APP by  $\alpha$ -secretase. The identification of proteins with  $\alpha$ -secretase activity is ongoing, and currently includes a constitutive activity [a disintegrin and metalloproteinase (ADAM)-10].<sup>22</sup> Because the  $\alpha$ -secretase cleavage site is within the A $\beta$  sequence of APP, and none of these proteolytic fragments have been associated with the generation of AD, enhanced cleavage at this site may represent a disease modifying strategy for AD as first postulated by Nitsch and colleagues.<sup>23</sup>

A related strategy to increase the fraction of APP cleaved by  $\alpha$ -secretase is to modulate the trafficking of APP in such a way as to increase the likelihood that  $\alpha$ -secretase will cleave APP. There are preliminary data that members of the sortin nexin family of proteins can reduce the rate of APP endocytosis, and increase sAPP $\alpha$  production, possibly by exposing the APP substrate to ADAM-10 for an extended period of time. Similarly, strategies that increase the production of ADAM-10 by inhibiting protease inhibitors such as tissue inhibitor of matrix metalloproteinase (TIMP) 1 and TIMP3 may represent further therapeutically tractable approaches to further shift the bias of APP processing from the amyloidogenic to the nonamyloidogenic pathway.<sup>3</sup>

### D. Inhibition of A $\beta$ aggregation

B-sheet breaker that could degrade A $\beta$  is a potential target for AD. Soto and colleagues designed a peptide (i $\beta$ A11) containing N-terminal domain of A $\beta$  that mainly contributes to A $\beta$  fibrillogenesis. This breaker can bind to A $\beta$  and block the interaction between monomers,

oligomers and prevent the formation of amyloid fibrils.<sup>24,25</sup>

Insulin-degrading enzyme (IDE) is a cytosolic metalloendopeptidase that hydrolyzes numerous peptides with poor substrate selectivity and specificity and was the first protease to be implicated in the proteolytic degradation of A $\beta$ .<sup>26</sup> IDE isolated from human brain extracts was demonstrated to cleave A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> preventing aggregation and neurotoxicity of A $\beta$  *in vitro*.<sup>27</sup> Genetic association with late-onset AD<sup>28</sup> and the correlation of high steady-state enzyme levels in brain areas less vulnerable to amyloid pathology in AD support the involvement of IDE in A $\beta$  degradation.<sup>29</sup>

Neprilysin (NEP) is a 90- to 100-kDa plasma membrane-bound, extracellular, metalloendopeptidase that preferentially hydrolyzes oligopeptides on the amino terminal of hydrophobic amino acid residues. NEP is expressed in brain and has been demonstrated to hydrolyze A $\beta$ <sub>42</sub> *in vitro* and *in vivo*.<sup>30,31</sup> A 50% reduction of cortical amyloid deposits in transgenic APP mice, after an intracerebral injection of a viral construct expressing NEP, provides further compelling evidence for a potential NEP-mediated A $\beta$ -clearance mechanism *in vivo*.<sup>32</sup> In addition, the recent observation that somatostatin regulates brain A $\beta$ <sub>42</sub> levels through the modulation of proteolytic degradation by NEP suggests a potential therapeutic strategy by targeting somatostatin receptors.<sup>33</sup>

Plasmin, a serine protease released after cleavage of the zymogen plasminogen, can also modulate the clearance of A $\beta$ .<sup>34</sup> Kinetic studies measuring the turnover rates of soluble and aggregated A $\beta$ , evaluation of A $\beta$  fibrils by electron microscopy, and A $\beta$  neuroprotection assays in rat cortical cultures, indicate that A $\beta$  is a plasmin substrate *in vitro*.<sup>35,36</sup> Decreased plasmin activity may explain reduced A $\beta$  degradation and accumulation of amyloid pathology in AD,<sup>37</sup> and strategies to elevate plasmin activity may be of therapeutic relevance.

Several anti-A $\beta$  aggregation agents are currently in clinical testing. Their mechanisms of action vary and are not completely understood, but are believed to involve prevention of fibril formation and facilitation of soluble A $\beta$  clearance. Tramiprosate (Neurochem, Inc.) is a small-molecule glycosaminoglycan (GAG) mimetic. Glycosaminoglycan binds to soluble A $\beta$ , facilitating fibril formation and deposition of amyloid plaque. GAG mimetics compete for GAG-binding sites, thereby blocking fibril formation and reducing soluble A $\beta$ . Colostrinin is a proline-rich polypeptide complex derived from sheep colostrum (O-CLN; ReGen Therapeutics). Colostrinin inhibits A $\beta$  aggregation and neurotoxicity in cellular assays and improves cognitive performance in laboratory animals.<sup>38,39</sup>

Metal ions like Cu<sup>2+</sup> and Zn<sup>2+</sup> may be involved in the mediation of A $\beta$  aggregation and toxicity. A significant decrease in brain A $\beta$  deposition in APP-transgenic mice

was observed after 9 weeks treatment with clioquinol, an antibiotic and Cu/Zn chelator that crosses the blood–brain barrier.<sup>40,41</sup>

### E. Immunotherapy

Immunotherapy has been demonstrated effectively in removal of proteins which accumulate abnormally in animal models of AD and other dementias. Several immunotherapies for AD have been tried in mouse models with transgenic Swedish mutant APP gene.<sup>42</sup> For most patients, A $\beta$ 42 immunization provides effective immune response and promotes amyloid plaques degradation. Immunization with the full-length A $\beta$ 42 peptide, containing both B and T cell epitopes, can be more effective in enhancing T cell activation to A $\beta$  clearance. It is desired to have Th2 immune response to promote antibody production and inhibit proinflammatory Th1 response that could activate imbroglia-induced cytokine release and neurotoxicity.<sup>43,44</sup>

DNA vaccination may open up a new avenue for treatment of AD. Ghochikyan et al. constructed a DNA minigene with A $\beta$ 42 fused to mouse interleukin-4 as a molecular adjuvant to generate anti-A $\beta$  antibodies. This compound successfully enhances the Th2 immune responses and induces the generation of IgG1 and IgG2b A $\beta$  antibodies recognize plaques.<sup>45</sup> Passive immunotherapy includes administration of specific  $\beta$  amyloid peptide antibodies that would bypass immune response and would not lead to T cell-mediated encephalitis.  $\beta$ -amyloid peptide antibodies (10D5) not only inhibit aggregation of A $\beta$  but also reduce plaque-induced neuritic alterations and cytotoxicity in APP [V717I] transgenic mouse model.<sup>46</sup>

Three different, though not mutually exclusive, mechanisms have been proposed to explain the amyloid lowering effect of A $\beta$  immunization. Following the detection of antibodies bound to brain amyloid deposits it has been postulated that they trigger Fc-receptor-mediated phagocytosis.<sup>47,48</sup> As an alternative mechanism, the antibodies might act as chaperones and disrupt A $\beta$  aggregates or prevent aggregation.<sup>49</sup> Finally, circulating antibodies were postulated to sequester A $\beta$ , shift the equilibrium towards the periphery and thereby reduce brain A $\beta$  deposition.<sup>50</sup>

## 2. Therapeutic strategies targeting tau

### A. Inhibition of tau kinase

Another pathological hallmark of AD is NFTs, which are composed of intracellular filamentous aggregates of hyperphosphorylated MT-associated tau protein, self-conversion into PHF-tau. Numerous mutations of tau gene have been detected in chromosome 17 that is linked to several forms of fronto-temporal dementias.<sup>51</sup> Dysfunction of tau proteins is responsible for the failure of the self-assembling tau to regulate the MT dynamics

that is essential for cell survival. Tau can be phosphorylated by several kinases including glycogen synthase kinase-3 $\beta$  (GSK3  $\beta$ ) and cyclin-dependent kinase 5 (CDK5) that can be regulated by A $\beta$  deposition.<sup>52,53</sup> Therefore, drugs targeting tau hyperphosphorylation and NFTs may benefit for slowing AD progression. Nearly 20 kinases are reported to phosphorylate tau *in vitro*; therefore exact identification of the relevant kinase(s) responsible for pathology has proven difficult. The rationale for developing therapeutic inhibitors for cdk-5 and GSK-3 activities has been reviewed elsewhere, but to our knowledge drug discovery studies remain preclinical at this time.<sup>54,55</sup>

Recent studies evaluating the cascade of events leading to neurofibrillary pathology suggest that hyperphosphorylation of tau by kinases such as cdk-5 and GSK-3 is preceded by phosphorylation of the tau microtubule binding domain by microtubule affinity regulating kinase (MARK). It is suggested that inhibition of MARK may block the event(s) triggering microtubule disruption, tau hyperphosphorylation, aggregation, formation of neurofibrillary tangles and neurodegeneration. Alternative exploratory strategies for reducing tau hyperphosphorylation include increasing the activity phosphatases such as protein phosphatase-2A, thereby promoting the enzymatic dephosphorylation of tau.<sup>56,57</sup>

### B. Activation of phosphatase

The phosphorylation state of any phosphoprotein results from the activities of both, kinases and phosphatases. It has been suggested, that in Alzheimer's disease, an imbalance of kinase and phosphatase activities may lead to abnormal hyperphosphorylation of tau protein. Memantine, an NMDA-receptor antagonist approved for the treatment of moderate to severe Alzheimer's disease was recently reported to inhibit okadaic acid-induced abnormal tau hyperphosphorylation and the associated neurodegeneration in rat hippocampal slices. Interestingly, it was suggested that memantine exerted this effect by restoration of PP2A activity through 'PP2A signalling'.<sup>58,59</sup>

## 3. Gene and stem cell therapy

Since nerve growth factor (NGF) was discovered to rescue cholinergic neurons from apoptosis in 1986, gene therapy with NGF, glial derived neurotrophic factor (GDNF), brain derived neurotrophic factor (BDNF) and neprilysin for the treatment of AD and related neurodegenerative disorders has been undergoing various experimental and clinical trials. These therapies have been reported not only effective in preventing degeneration of cholinergic neurons but also in ameliorating behavioural deficit and memory impairment in animal models of AD. However, it is a challenge to establish a delivery system that is safe, high efficacy and simple.<sup>60,61</sup>

Stem cells are another potential resource of therapy for the treatment of AD because of its ability to differentiate into all kinds of neuronal cells. In animal models of AD, stem cell transplantation has showed some promising results in preventing disease progression.<sup>62,63</sup>

## CONCLUSIONS AND RECOMMENDATIONS

To sum up, the currently available drugs (ChEIs and memantine) offer symptomatic relief that is temporary at best. New and more durable disease-modifying treatments are needed. The widespread acceptance of the amyloid hypothesis has spurred intense research efforts to identify disease-modifying treatments that interrupt the natural course of Alzheimer's disease by blocking the pathologic processing of APP to A $\beta$ <sub>42</sub> or enhancing its clearance or decreasing its toxicity. Molecular milestones along the amyloid pathway, including APP, the enzymes involved in generating A $\beta$ <sub>42</sub> (i.e.,  $\gamma$ -secretase,  $\beta$ -secretase) or less toxic derivatives (i.e.,  $\alpha$ -secretase), and A $\beta$ <sub>42</sub> itself, are promising targets for therapeutic intervention. Therefore, prospects for the future of Alzheimer's disease treatment are very encouraging. The diversity of different therapeutic strategies being explored in clinical trials offers hope. In the not too distant future, disease-modifying treatments will become the standard of care and serve as the springboard for permanently changing the course of Alzheimer's disease. Last yet most importantly, as this review has explored numerous areas for intervention, in the future, more clinical trials are needed to put this chronic disease under control by halting its progression fully and also attempting a cure as much as possible.

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