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Drug Development for Alzheimer's Disease: Recent Progress

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ABSTRACT

Alzheimer's disease, the most common cause of dementia, is characterized by two major pathological hallmarks: amyloid plaques and neurofibrillary tangles. Based on these two indicators, an amyloid cascade hypothesis was proposed, and accordingly, most current therapeutic approaches are now focused on the removal of β-amyloid peptides (Aβ from the brain. Additionally, strategies for blocking tau hyperphosphorylation and aggregation have been suggested, including the development of drugs that can block the formation of tangles. However, there are no true disease-modifying drugs in the current market, though many drugs based on theories other than Aβ and tau pathology are under development. The purpose of this review was to provide information on the current development of AD drugs and to discuss the issues related to drug development.

Key words: Alzheimer's disease, Aβ, tau, drug, clinical trial

INTRODUCTION

In the last century, the world transitioned from a young to aging population that increasingly suffers from major health problems such as infectious disease to chronic illness. Especially, neurodegenerative diseases are a major concern in aged countries. Among these diseases, Alzheimer's disease (AD) is the most prevalent with the number of the patients about 30 million worldwide, and this will reach more than 80 million in 2040 (Prince and Jackson, 2009).

AD, the most common cause of dementia, is a chronic disorder characterized by a progressive decline in cognitive function. Major pathological hallmarks include extensive neuronal loss, formation of intracellular neurofibrillary tangles (NFT) and extracellular deposition of β-amyloid peptides (Aβ). Despite extensive research, the cause of sporadic AD (more than 90% of all AD) is still unknown (Brunden et al., 2009; Bettens et al., 2010). Additionally, there are no true disease-modifying drugs in the market; drugs currently available are acetylcholine esterase inhibitors and a N-methyl D-aspartic acid (NMDA) receptor modulator, which are for symptomatic treatments only (Mangialasche et al., 2010).

Amyloid cascade theory and tauopathy have been proposed as the cause of AD based on two pathological hallmarks (NFT and Aβ). Accordingly, drug development has focused on the removal of

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Aβ and NFT from the brain. However, many drugs are currently under development based on other theories of the etiology of AD. Disease-modifying treatments are highly desirable but are thus far unsuccessful. The failed efficacy of recent multi-center clinical trials could be due to systematic and random measurement errors, as well as improper design, monitoring, analysis and interpretation (Becker and Greig, 2008). However, several of the compounds currently being developed could become drugs with additional technical innovations and methodological improvements for clinical trials.

The purpose of this article was to provide a brief overview on the current development of drugs for Alzheimer's disease and offer some prospective comments.

DRUG DEVELOPMENT TO TARGET Aβ (TABLE 1)

The amyloid cascade hypothesis is a compelling model that the aberrant production of Aβ 1-42 is the causative agent in the pathogenesis of AD. There are many strategic approaches to reduce the level of toxic Aβ 1-42 in the brain: (1) immunotherapy, (2) γ-secretase inhibitors, (3) β-secretase inhibitors, (4) Aβ oligomerization inhibitors, (5) inhibitors that prevent transport of Aβ from blood to the brain, (6) degradation of Aβ.

Immunotherapy

Several immunotherapies targeting Aβ have been conducted in clinical trials based on previous data on improved cognition in mouse models of AD (Dodart et al., 2002; Kotilinek et al., 2002; Lee et al., 2006). The first generation vaccine targeting Aβ was AN-1792, but its phase II clinical trial (CT) was discontinued due to the development of aseptic meningoencephalitis in 6% of patients (Gilman et al., 2005). The second-generation vaccine, ACC-001, was developed to avoid an inflammatory response and currently undergoing phase II CTs (Fagan, 2008a).

Passive immunizations have also been attempted. Among them, bapineuzumab, a humanized monoclonal antibody targeting Aβ, completed its phase II trial in 234 mild to moderate AD patients. Although it failed to show a clear clinical benefit, it moved to phase III CTs based on its safety and biomarker data generated by positron emission tomography (PET) (Strobel, 2008a). Recently its highest dose (2 mg/kg) was abandoned to reduce the risk for vasogenic edema (Strobel, 2009) but the interim data of phase III show reduction of

Table 1. AD Drug development to target Ab or tau

Agent	Phase	Mechanism of action
ACC-001	II	Immunotherapy (active), Aβ amino-terminal conjugate
Bapineuzumab (AAB-001)	III	Immunotherapy (passive), anti-Aβ aminoteminal MAb*
Solanezumab (LY2062430)	III	Immunotherapy (passive), anti-Aβ mid-region MAb
PF-04360365	II	Immunotherapy (passive), anti-Aβ MAb
Gammagard	III	Immunotherapy (passive), intraveneous immunoglobulin
Semagasestat (LY450139)**	III	γ-secretase inhibitor
Begacestat (GSI-953)	I	γ-secretase inhibitor
Flurizan (tarenflurbil)**	III	γ-secretase modulator
CTS-21166	II	β-secretase inhibitor
TAK-0707	Preclinical	β-secretase modulator
ELND005 (AZD 103)	II	Aβ oligomer formation breaker
PBT2	II	Amyloid fibril formation breaker
PF-04494700 (TTP488)	II	RAGE inhibitor
PAZ-417	I	PAI-1 inhibitor, degradation of Aβ
Valproic acid**	III	GSK inhibitor
Lithium	II	GSK inhibitor
NP-031112 (NP-12)	II	GSK inhibitor
Rember (methylthioninium chloride)	II	Preventing tau aggregation
Davunetide (AL-108 and AL-208)	II	Preventing tau phosphorylation

*MAb: monoclonal antibody, **Clinical trial (s) was failed. See the text.

amyloid load in the brains (Landhuis, 2010b). Like bapineuzumab, LY2062430 (Solanezumab) and PF-04360365 are monoclonal antibodies against Aβ peptide. The former completed its phase I and II trials and is currently in phase III (Siemers et al., 2010; CT 1 and CT 2 in ref.), whereas the latter completed phase I CTs and is undergoing phase II (Landhuis, 2009a; CT 3 in ref.).

Since a mixture of intravenous immunoglobulin (IVIg) of human blood contains the antibody against Aβ it could be used to quench a pool of Aβ (Dodel et al., 2002). In a small trial (24 people) for 18 months, IVIg (Gammagard) slowed clinical decline and protected brains against shrinkage. The mechanism for protection against AD could be due to direct targeting of Aβ by IVIg or an indirect immunomodulatory effect. A larger (360 AD patients) multi-center phase III trial is underway (Dodel et al., 2010; Fagan, 2010e). There are several active (AFFITOPE AD01 and AFFITOPE AD02, GSK933776A, MABT5102A and V950) as well as passive (R1450 and RN 1219) immunizations for Aβ under development currently (Lemere and Masliah, 2010).

γ-secretase inhibitors

Gamma-secretase is the final enzyme involved in the cleavage of amyloid precursor protein (APP) in the membrane, and it consists of a complex of four different proteins (presenilin, nicastrin, Aph-1 and Pen-2) (Takasugi et al., 2003; Wolfe, 2008). Among the four proteins in the complex, presenilin is the key enzyme that cleaves APP. However, γ-secretase cleaves other proteins (more than 50 protein substrates) in addition to APP, which makes finding an APP-specific inhibitor for γ-secretase very difficult (Beel and Sanders, 2008). Furthermore, presenilin is an unusual protein with more than 150 mutations in its gene that are autosomal dominant for the early onset of AD (PS1 mutation database in ref.). Many mutations discovered in earlier studies increase the release of Aβ 42, a neurotoxic form of Aβ peptides, in the brain. Accordingly, strategies for blocking its enzymatic activity have been intensely pursued. Regarding γ-secretase, substrate specificity is challenging because it cleaves many substrates such as Notch, which is an important regulator in many physiological processes (De Strooper et al., 1999).

The first *in vivo* proof of γ-secretase as a therapeutic target of AD was obtained using DAPT in a transgenic mouse model, which resulted in reduced Aβ in the brain after oral administration (Dovey et al., 2001; Lanz et al., 2003). LY411575 showed adverse effects on the immune system and intestine in a mouse model, and it was later found to have poor selectivity for APP over Notch (Wong et al., 2004). Additionally, the side effects of LY411575 have prevented the viability of a clinical trial. Later, LY450139 (Semagacestat) was developed to avoid such adverse side effects. Phase II trials with LY450139 was unusual to estimate the clinical endpoint by measuring biomarkers (e. g. the plasma concentration of Aβ) rather than measuring the cognitive or clinical improvements (Strobel, 2007b). Even though LY450139 did not have excellent selectivity for APP over Notch (E50=1 : 2.8), it did move on to phase III trials but halted due to the treatment group showing faster decline in cognition than the placebo group (Strobel, 2007a; Martone et al., 2009; Fagan, 2010d).

BMS-299897 and MRK-560 were developed for improvement of substrate selectivity of γ-secretase, and they have been shown to be effective in animal models without any sign of Notch inhibition (Barten et al., 2005; Best et al., 2007). However, they were not found in the stage of clinical trials. GSI-953 (Begacestat) also has excellent selectivity for APP cleavage over Notch (E50=1 : 16.8) (Mayer et al., 2008). Phase I CTs for GSI-953 have been conducted but no data have been disclosed.

In addition to classical inhibitor approaches, compounds that modulate the enzymatic activity of γ-secretase have been developed. Certain non-steroidal anti-inflammatory drugs (NSAIDs) have been found to reduce the amount of toxic Aβ 42 (McGeer and McGeer, 2007). For instance, tarenflurbil (Flurizan), which is the R-form of flurbiprofen lacking COX-inhibitory activities, was the first γ-secretase modulator to be developed (Eriksen et al., 2003; Kukar et al., 2007). Tarenflurbil showed promising outcomes in early preclinical and clinical trials. However, it failed to show any difference compared to the placebo group in phase III CTs (Green et al., 2009). This failure could have been due to an insufficient amount of tarenflurbil in

the brain, as an earlier study (21-day) did not reduce Aβ42 in the plasma or cerebrospinal fluid (CSF) (Galasko et al., 2007).

Recent data suggest that the mechanism by which γ-secretase modulates NSAIDs could be based on binding of the substrate (APP in this case) rather than γ-secretase itself. Binding of the compounds to APP prevents dimerization of APP and shifts the cleavage site such that less toxic Aβ fragments are produced (Richter et al., 2010).

Carriers of mutations in the presenilin gene share heterogeneity among their pathological phenotypes. At the time of its discovery, it was suggested that the presenilin gene undergoes gain-of-function mutations, but since then more than 150 mutations have been identified (PS1 mutation database in ref.). Many of the mutations were found to be reduction-of-function by *in vitro* assays involving simpler organisms such as *C. elegans* (Okochi et al., 2000; Wolfe, 2007). Moreover, conditional knockout of PS1 in postnatal forebrain leads to cognitive deficit in the mouse, suggesting that PS1 is required for normal neuronal function in the adults (Yu et al., 2001). This could be a significant factor in the development of γ-seretase inhibitors, and the cause of recent failures in CTs with γ-secretase inhibitors could be due to the disturbance of normal presenilin functions.

BACE inhibitors

Beta-site amyloid precursor protein cleaving enzyme (BACE1) was cloned to measure the enzymatic activity of β-secretase, which is the enzyme responsible for initiating Aβ generation (For review, Cole and Vassar, 2008). Thus, BACE is one of the best drug targets for the therapeutic inhibition of Aβ production. Moreover, it is considered to be a better target than γ-seretase for disease-modifying drugs since the knockout mouse of BACE1 does not produce Aβ and shows only minor behavioral changes (Cai et al., 2001; Roberds et al., 2001). Even though the structure of BACE1 has been solved, the design of potent inhibitors is still problematic since the active site is so large (Hong et al., 2000). CTS-21166 (CoMentis) is the first BACE1 inhibitor tested in phase I CTs. According to information provided by the company, CTS-21166 is safe, well-tolerated and shows dose-related reduction in plasma Aβ 40 (Strobel, 2008c).

LY2811376, another orally available and brain-penetrant inhibitor, showed good tolerance and dose-dependent reduction of plasma Aβ in phase I CTs. However, its trials were terminated due to additional non-clinical toxicology data which was found in the middle of the CTs. Nonetheless, it was clearly demonstrated that BACE1 is a druggable target (Rogers, 2010). TAK-0707, a promising non-peptidic and lipophilic compound, is non-competitive for substrates and results in reduction of Aβ and cognitive improvement in a mouse AD model (Fukumoto et al., 2010). However, no CT on TAK-0707 is being currently conducted. Other compounds which are derived from peptidomimetics and non-peptides have nano-molar potency in *in vitro* assays. However, they lack *in vivo* efficacy data in mouse models. (Hills and Vacca, 2007)

Alternatively, compounds that modulate the activity of β-secretase could be candidates for AD therapeutics. Posiphen is enantiomer of phenserine and is inactive in inhibiting acetylcholine esterase while phenserine has cholinergic activity (see below). Posiphen reduces both Aβ 40 and Aβ 42 in mice and it acts by reducing β-secretase activity as well as that of APP transcription (Lahiri et al., 2007). Recently, recruitment is ongoing for a phase I study in subjects with amnestic mild cognitive impairment (CT 4 in ref.).

The recent discovery that BACE1-knockout mice produce excess sodium channels in their axons, have increased neuronal excitability, and are more susceptible to seizures than normal mice sends a caution to the developers of BACE1 inhibitors (Hu et al., 2010).

Aβ oligomerization inhibitors

Tramiprosate binds to soluble Aβ and prevents formation of amyloid plaques (Gervais et al., 2001). This drug was the first to have been developed based on amyloid cascade theory, reaching late-stage development. However, the outcome of its phase III CTs was not conclusive despite promising results in phase II (Wong, 2007). These poor results could have been due to its promotion of tau aggregation or unusually large placebo response rate (Santa-Maria, 2007; Wong, 2007).

Phenserine was developed as an inhibitor of acetylcholine esterase and later demonstrated cognitive improvement in animal models. Use of phenserine reduced the amount of APP by modulating APP translation through interaction with the 5'UTR. Even though moderate success was attained in phase II, the drug failed to show any significant benefit over placebo in phase III trials (Strobel, 2005). ELND005 (formerly known as AZD 103) is a scillo-inositol, one of the 8 possible stereoisomeric forms of inositol. It reduced the accumulation of Aβ oligomers and suppressed memory loss in transgenic mice (Hawkes et al., 2010). Long-term phase II trials using ELND005 did not show significant improvements in cognition even though they showed the effects on CSF Aβ (Fagan, 2010c). PBT2, an anti-fibrillar agent, is a metal-protein-attenuating compound that alters the interaction between Aβ and metals. The phase IIa trial of PBT2 showed the reduction of Aβ 42 in CSF without affecting the plasma biomarkers of AD. Even though no major adverse effects were observed, cognitive improvement was restricted to a part of executive functions (Lannfelt et al., 2008).

Inhibitors of Aβ transport: RAGE inhibitors

The receptor for advanced glycation end products (RAGE) binds Aβ and transports it from plasma to the brain via the blood-brain barrier (Deane et al., 2003). Thus, RAGE has been suggested as a therapeutic target for preventing the accumulation of Aβ in the brain. PF-04494700 (formerly TTP488), the first RAGE inhibitor for AD, was recently developed. Phase II CTs for evaluation of safety and tolerance have been completed. Currently, phase II for efficacy is underway but subjects have not been recruited (CT 5 in ref.).

Degradation of Aβ

Degradation of Aβ could be the most effective strategy for its removal from the brain. There are some proteases that degrade Aβ, as evidenced *in vivo* using knock-out or over-expressing transgenic mice. Such proteases are insulin-degrading enzymes, including neprilysin and plasmin activator inhibitor-1 (PAI-1) inhibitor. The development of compounds that enhance the degradation of Aβ is still in the exploratory stage. The only compound that has reached CTs is PAZ-417, a PAI-1 inhibitor (Jacobsen et al., 2008). Despite the possibility of bleeding by activation of the plasmin system, there were no severe side effects in any animal model. Two phase I trials have been completed while a third was terminated (CT 6 in ref.).

DRUG DEVELOPMENT FOR TARGETING OF TAU PROTEIN

Even if Aβ is considered to be the major cause of AD pathology, tau could play an important role in AD pathogenesis (Iwatsubo, 2006). Therefore, blocking tau could be an effective therapeutic strategy. Tau is a protein found in the cytoplasm that binds to tubulin for the stabilization of microtubules. During AD, tau is hyperphosphorylated, resulting in NFTs inside neurons, which are toxic to neurons (Iqbal et al., 1994). Kinases that are involved in the hyperphosphorylation of tau are considered as drug targets. However, there are not many drug candidates compared to those of Aβ pathology.

A major therapeutic approach for tau pathology is developing inhibitors of kinases of tau hyperphosphorylation. Several kinases are reported to phosphorylate tau protein, including Glycogen synthase kinase 3β (GSK3β), cyclin-dependent kinase 5 (CDK5), extracellular signal-regulated kinase (ERK), P38 and c-Jun N-terminal kinase (JNK) (Iwatsubo, 2006). Two well known drugs for psychiatric disorders, valproic acid and lithium, inhibit GSK3 and reduce tau phosphorylation. Although valproic acid reached phase III CTs, it failed to show any improvement of neuropsychiatric symptoms in AD patients (Landhuis, 2009a). Lithium also failed to show any change in CSF markers or cognitive improvement in a small trial (Hampel et al., 2009).

Among the several GSK3 inhibitors under development, NP-031112 (NP-12), which is non-competitive to ATP, reduces tau phosphorylation and amyloid deposits in the brain of animal models (Sereno et al., 2009). A phase II trial with this drug has been completed, but the result has not been published.

Alternatively, there are approaches preventing tau aggregation or promoting aggregate disassembly.

Methylthioninium chloride (methylene blue, Rember), a widely used dye for protein staining, interferes with tau aggregation and also enhances mitochondrial function. Phase II trials showed slow disease progression, but efficacy and safety still need to be confirmed in phase III CTs (Strobel, 2008b).

Davunetide has been developed as both an intranasally administered peptide of 8 amino acids (AL-108, NAP) and as an intravenous formulation (AL-208). Although the neuroprotective mechanism is not clear, AL108 inhibits tau hyperphosphorylation and protects the brain from Aβ toxicity in animal models (Matzuoka et al., 2007). A phase II study on AL-108 in patients with amnestic mild cognitive impairment showed positive effects on cognitive function (Fagan, 2009a). However, the study was short (12 weeks) and needs to be confirmed by additional studies.

DRUG DEVELOPMENT BASED ON OTHER THEORIES (TABLE 2)

Dimebon, which was developed as a non-selective antihistamine, weakly inhibits acethylcholine esterase (Bachurin et al., 2001). It also inhibits NMDA receptors and voltage-gated calcium channels, but its neuroprotective activity is mainly derived from the enhancement of mitochondrial function (Bachurin et al., 2003). A phase II CT in 2007 showed clear improvement for all outcome measures (Doody et al., 2008). However, the same positive results were not confirmed in phase III trials (Fagan, 2010a).

Since AD patients show reduced insulin signaling in the brain and diabetes increases the risk of developing dementia, there are many approaches to increase insulin in the brain. Recently, a four-month phase II study on intranasal administration of insulin in patients with MCI or early AD showed improved cognition and daily function, with larger phase III trials planned (Landhuis, 2010a). Insulin-like growth factor-1 (IGF-1) is also considered a treatment for neurodegenerative disorders. However, MK-677 (ibutamoren mesylate), a potent inducer of IGF-1 secretion, did not benefit AD patients (Sevigny et al., 2008). Recent data from IGF-1 receptor knockout mouse is more confusing: the results suggested that reducing insulin/IGF-1 signaling helps avoid dementia (Fagan, 2009b). A clinical trial to assess the relationship between the levels of IGF-1 system components and cognitive status in patients with AD is underway (CT 7). Drugs that modulate insulin signaling have also been developed. However, rosiglitazone and pioglitazone, both peroxisome proliferator-activated receptor-γ (PPARγ) agonists, did not show significant benefits in patients with mild to moderate AD (Strobel, 2006).

Table 2. AD Drug development based on other theories

Agent	Phase	Mechanism of action
Dimebon**	III	Enhancement of mitochondria function
Insulin (intranasal)	II	Increase insulin signal
Gikgo biloba**	III	Neuroprotection
Huperzine A	II	Neuroprotection and acethylcholine inhibition
Atorvastatin**	III	Cholesterol-lowering
NSAID**	III	Preventing inflammation in brain
MK-0952	II	Phosphodiesterase 4 inhibitor
PF-0447943	I	Phosphodiesterase 9A inhibitor
Vitamin E*	III	Anti-oxidation
Omega-3*	III	Unsaturated fatty acid

*The result of CT was inconclusive, **Clinical trial(s) was failed. See the text.

Ginkgo biloba is an herb that is widely used to prevent and treat cognitive decline in aging people. However, CTs conducted for six years (2002～2008) showed that daily doses of standardized ginkgo biloba leaf extract failed to delay the development of AD in 1,545 treated seniors (Dekosky et al., 2008). Huperzine A is a natural alkaloid compound with neuroprotective effects in addition to inhibitory activity of acetylcholine esterase. Despite positive results in phase II CTs, further trials are not ongoing (Wang et al., 2009).

Elevated levels of cholesterol are associated with a risk of AD (Kivipelto and Solomon, 2006), and cholesterol-lowering statins have been suggested to reduce the risk of AD. A transgenic mouse model was used to demonstrate that a high level of cholesterol increases the production of Aβ (Refolo et al., 2000). However, clinical studies on treatment with statins in patients with AD have not produced any beneficial effects so far. Atorvastatin failed to show any benefit in phase III trials (Feldman et al., 2010), and trials with pitavastatin or simvastatin for the prevention and therapy of AD are ongoing

(Fagan, 2008b).

Epidemiological data and a neuroinflammation model of AD suggest that NSAID can be effective for the treatment and prevention of AD (Townsend and Pratico, 2005; Tuppo and Arias, 2005). To find the relationship between NSAIDs and AD, four prospective clinical studies were conducted and they showed a reduced risk for AD upon treatment with NSAIDs. However, double blind randomized CTs with placebo groups failed to show that NSAID is an effective treatment for prevention of AD (ADAPT Research Group, 2009). Recent data suggest the prevention should be done in very early stage of AD (Varvel et al., 2009).

Antagonists or agonists of many neurotransmitter receptors have been suggested as drug candidates for AD (Doraiswamy and Xiong, 2006), including SB-742457 (serotonergic, 5-HT_6 receptor antagonist; Maher-Edwards et al., 2010), PRX-03140 (5-HT_4 agonist, terminated), SR57746A (xaliproden) and Lecozotan SR (5-HT_{1A} receptor antagonist, lack of efficacy), SGS-742 ($GABA_B$-receptor antagonist, unsuccessful), AZD3480 ($\alpha 4\beta 2$-selective neuronal nicotinic receptor agonist; Dunbar et al., 2010), CX717 (AMPA-type glutamate receptor modulator; Hampson et al., 2009) and RO5313534 (MEM 3454, nicotinic $\alpha 7$ receptor agonist; Rezvani et al., 2009).

Phosphodiesterase 4 inhibitors show neuroprotective and neurorengenerative activities in a mouse AD model. MK-0952 completed phase II trials in patients with mild to moderate AD, but the results have not been published and no further clinical trials are going (CT 8). PF-04447943, which is a selective phosphodiesterase 9A inhibitor, was tested for its AD therapeutic efficacy. Phase I was completed, and currently AD patients are recruiting for phase II CTs (Fagan, 2010b).

Women have higher risk than men for AD. It could be due to changes in hormonal regulation after menopause. Modulation of hormones has been suggested as a treatment for AD in women. Raloxifene, a selective estrogen receptor modulator, was tested for the prevention of cognitive decline in postmenopausal women with osteoporosis. High dose (120 mg/day) of raloxifen reduced the risk of mild cognitive impairment (Yaffe et al., 2005; Legault et al., 2009). However, no further development was reported for the drug in the prevention of AD.

Nerve growth factor (NGF) supports survival and fiber outgrowth of basal forebrain cholinergic neurons, and data suggest NGF imbalance activates the production of Aβ, leading to neurodegeneration in AD patients (Cattaneo et al., 2008). There have been many attempts to deliver NGF to basal forebrain cholinergic neurons. However, intracerebroventricular infusion of NGF was interrupted by adverse effects (Eriksdotter Jonhagen et al., 1998). Nonetheless, intracerebral injection of genetically modified cells producing NGF showed an overall lower rate of cognitive decline (Tuszynski et al., 2005). Encapsulated biodelivery of NGF cholinergic basal forebrain neurons was also attempted, and it increases expression of nicotinic receptors and cognitive improvement (Eriksdotte et al., 2010).

Neuroreplacement therapies for neurodegenerative diseases based on stem cells have also been suggested (Sugaya and Merchant, 2008). Other approaches involving vitamin E or omega-3 polyunsaturated fatty acids have also been attempted but the results were inconclusive (Freund-Levi et al., 2006; Bjelakovic et al., 2007). Resveratrol, a phenolic compound derived from grapes and red wine, has neuroprotective effects and has been suggested for AD therapeutics (Sun et al., 2010).

CONCLUSION

AD is a complex, multi-factorial disorder, the mechanism of which has not been fully understood. After considerable success in the drug development of symptomatic AD treatments, the clinical development of new drugs for treatment of AD has resulted only in disappointment. Considering recent failures in clinical trials, more innovative approaches are greatly needed. Approaches based on a single target should be revised because there are several levels of interactions (especially environment) in AD pathogenesis. Therefore, mutli-target therapies should be considered more seriously, with mitochondrial protection and multi-target directed ligands serving as recent examples.

Most of the positive results in AD animal models have not been recapitulated in clinical trials, which implies that the current animal models for AD drug

development should be reconsidered. Especially, rodent models might have a more powerful ability to recover brain cells compared to that of human brain (Harrison et al., 2010).

Many studies suggest that certain lifestyle factors could modify the risk of developing AD. Among them, physical exercise may be an effective way to reduce the risk of AD. It has been demonstrated that physical exercise increases the many factors involved in neurogenesis (e.g. BDNF, TrkB, CREB, IGF-1), contribute to Aβ clearance, and improve cognition in animals (Vaynman et al., 2003; Ploughman et al., 2007).

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