

# Pharmacological Treatment for Alzheimer's Disease : Current Approaches and Future Strategies

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## Abstract-

More than a decade after the first approval of the use of acetylcholine esterase inhibitor on patients with Alzheimer's disease, we still not have a single treatment or combination therapy that can effectively stop or reverse the relentless progression of such neurodegenerative disease. Recently therapeutics targeting amyloid hypothesis have undergone scrutiny by many clinical trials. These include gamma secretase inhibitor for reducing beta amyloid formation, agents for preventing aggregation of amyloid oligomers, and immunotherapy for enhancing clearance of amyloid and plaque. Therapies targeting hyperphosphorylated tau is another promising mechanism to be tackled with. Other agents enforcing mitochondria functions, enhancing serotonin receptors, modulating advanced glycation end products, and neurotrophic factors, as well as other therapies are also emerging. We review current treatments and therapeutic strategies already undergone different stage of clinical trails in this report.

We propose that therapeutics of various combination composed of symptomatic treatments and disease modifying therapies will become standard regimens of AD treatment with much better efficacy than current approaches.

**Key Words:** amyloid hypothesis, tau protein, cholinesterase inhibitor, disease modifying therapy, combination therapy

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## INTRODUCTION

Alzheimer's disease (AD) is the most common progressive dementia in the elderly population. It is a chronic neurodegenerative disease characterized by brain atrophy, loss of neurons and loss of synaptic function secondary to amyloid plaque and neurofibrillary tangle (NFT) formation<sup>(1)</sup>. Currently there are no cura-

tive treatments or effective disease-modifying therapies even 14 years after the initial Food Drug Administration (FDA) approval of donepezil, the most commonly prescribed acetylcholine esterase inhibitor (AChEI). The article will review the current approaches and future strategies combating the debilitating, age-related progressive brain disease.

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## Current Approaches

There are only 5 medications approved by FDA to treat AD. They include 4 AChEIs and one N-methyl-d-aspartate (NMDA) antagonist.

### Cholinesterase inhibitors

The cholinergic hypothesis of AD concludes that cholinergic system in the basal forebrain are affected early in the disease process including loss of acetylcholine neurons, loss of enzymatic function for acetylcholine synthesis and degradation, resulting in memory loss<sup>(2)</sup> as well as deterioration of other cognitive and non-cognitive functions such as neuropsychiatric symptoms<sup>(3-5)</sup>. A strategy to enhance the cholinergic transmission by using AChEIs to delay the degradation of acetylcholine between the synaptic cleft was then proposed. In 1993 the first FDA approved AChEI, tacrine boomed out but it was no longer used because of its high prevalence of hepatotoxicity<sup>(6-8)</sup>. FDA approved another three AChEIs: donepezil (1996), rivastigmine (2000), and galantamine (2001) in the following years.

These drugs have been regarded as the standard and first-line treatment for AD. Systemic reviews including many double-blinded, randomized, placebo-controlled trials (RCT) of these three AChEIs all showed benefit on cognitive functions, activities of daily living (ADL), and global function for patients with mild to moderate AD; there was no significant difference of efficacy between individual AChEI<sup>(9-17)</sup>. Donepezil is also beneficial for severe AD.

Systemic reviews showed that the incidence of gastrointestinal adverse effect, such as nausea, vomiting, diarrhea and abdominal cramp, was lower with donepezil than with rivastigmine and galantamine<sup>(18,19)</sup>. The incidence of adverse effect was associated with higher therapeutic dose<sup>(20)</sup>. However, it may be that galantamine and rivastigmine match donepezil in tolerability if a careful and gradual titration routine over more than 3 months is used<sup>(19)</sup>. The dermal form of rivastigmine suggested lower dose with less adverse effect but comparable efficacy which was preferred by some caregivers<sup>(21,22)</sup>.

The long-term efficacy of AChEIs remains contro-

versial<sup>(23,24)</sup>, but continuing treatment was beneficial and was suggested if well-tolerated<sup>(25-28)</sup>. The efficacy of AChEI in protecting subjects with mild cognitive impairment (MCI) from converting into AD remains inconclusive<sup>(29)</sup>.

### Prevent NMDA regulated excitotoxicity

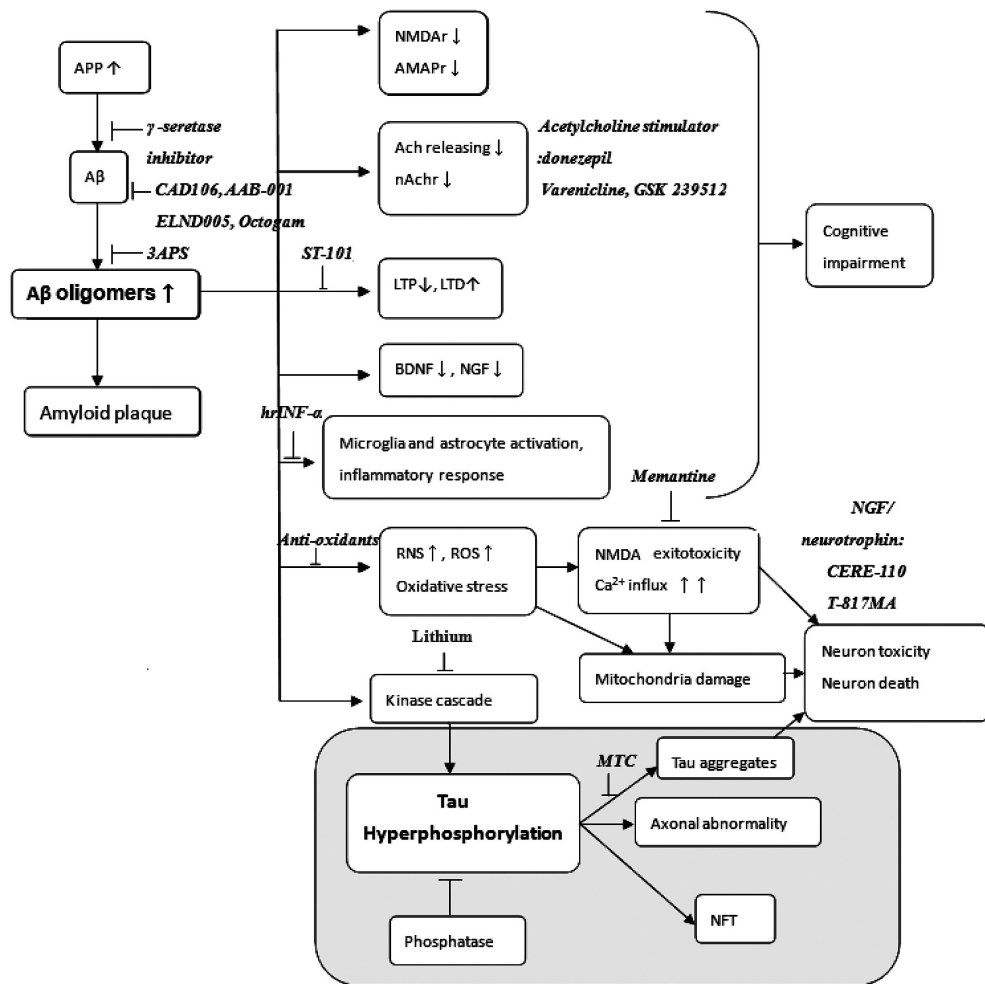
In addition to the conventional cholinergic hypothesis of AD, there is great evidence that NMDA regulated excitotoxicity, closely related to neuronal plasticity and memory function, plays an important role in neurodegeneration. Amyloid beta (A $\beta$ ) disturbs function of the postsynaptic NMDA receptor leading to excessive calcium influx into neurons and activation of NMDA-dependent downstream pathways. The cytosol and mitochondrial calcium overload results in a cascade of oxidative cytotoxicity and apoptosis<sup>(30,31)</sup>. Memantine, a voltage-gated and uncompetitive NMDA antagonist with moderate affinity, can protect neurons from excitotoxicity. It was approved by FDA in 2003 for treatment of the patients with moderate to severe AD. A $\beta$  disturbs NMDA receptor-dependent long-term potentiation (LTP) in the area 1 of Cornu Ammonis (CA1) and dentate gyrus both in vivo and in vitro<sup>(32)</sup>. NR2B (a subunit of NMDA receptor) plays a role in neuroplasticity and learning that reduces NR2B expression increasing the risk of AD. While enhancing activity of NR2B containing NMDA receptor may restore the memory function<sup>(33)</sup>.

### Memantine

A systemic review of double-blinded, parallel-group, RCT studies of memantine showed improvement in cognitive function, ADL and behaviors in people with moderate to severe AD after 6 months<sup>(34)</sup>. The memantine was usually well tolerated, except small group of patients might develop agitation. Another systemic review included 6 RCT studies indicated that memantine may reduce behavioral and psychological symptoms of dementia<sup>(35)</sup>.

### Combination therapy

RCT studies on parallel groups of patients with mod-



**Figure 1.** Treatment strategies based on amyloid cascade and tau hyperphosphorylation; APP: amyloid precursor protein, A $\beta$ : amyloid beta, NMDAR: N-methyl-D-aspartic acid receptor, AMPAR:  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, LTP: long-term potentiation, LTD: long-term depression, BDNF: brain-derived neurotrophic factor, NGF: nerve growth factor, RNS: reactive nitrogen species, ROS: reactive oxygen species, Ach: acetylcholine, nAChr: nicotinic acetylcholine receptor, NFT: neurofibrillary tangle, MTC: methylthionium chloride.

erate to severe AD showed a significant benefit in cognitive function, language, ADL, behaviors and global state from combination use of memantine and donepezil over placebo group (memantine and placebo)<sup>(36-39)</sup>. But such benefit was not demonstrated in patients with mild to moderate AD<sup>(40-41)</sup>. Atri et al. stated that combination therapy might slow down cognitive and functional decline in patients with probable AD compared with AChEI monotherapy or no treatment in a long-term observation study<sup>(42)</sup>. The DOMINO-AD protocol, a

pragmatic, 15-center, double-blind, RCT study on 800 patients with moderate to severe AD, randomized into one of the four groups (memantine + donepezil, memantine + placebo, donepezil + placebo, placebos), lasting at least for one year will evaluate cognition, ADL, non-cognitive dementia symptoms, quality of life, and caregiver burden. In this study, all participants will be subsequently followed for 3 years by telephone interview to record incidence of institutionalization. The study will elucidate the value of such combination therapy.

### Agents currently under investigation

Numerous studies focused on disease modifying therapeutics targeting anti-A $\beta$ , anti-oxidative injury, anti-inflammatory or anti-tau-phosphorylation strategies against the pathogenesis of AD. The following is a brief review of these potential drugs that are currently under or have just completed their phase III or phase II clinical trials.

#### *Drugs Targeting Amyloid*

##### *Drugs decreasing amyloid formation*

###### *$\Gamma$ -secretase inhibitor*

A $\beta$  oligomers consisting of 2-16 A $\beta$  peptides may result in synaptic dysfunction, LTP impairment, tau hyperphosphorylation and consequent oxidative neuronal death<sup>(43-45)</sup>. All these contribute to the cognitive defect of AD. A $\beta$  peptide comes from amyloid precursor protein (APP), an intra-membranous protein, catalyzed by  $\beta$ -secretase (BACE-1) and then  $\gamma$ -secretase. Thus blocking A $\beta$  formation may show potential benefit for AD treatment.

LY450139, Semagacestat, a  $\gamma$ -secretase inhibitor can inhibit A $\beta$  generation. Clinical trials have shown dose-dependent decrease of the plasma but not the CSF A $\beta$ <sup>(46-47)</sup>. Semagacestat had no cognitive or functional benefit for patients with mild to moderate AD in a multi-center, RCT phase II studies<sup>(48)</sup>. It is disappointing that preliminary results from two phase-III clinical trials (IDENTIY and IDENTITY-2) showed that Semagacestat did not slow down disease progression and was associated with worsening of clinical measures of cognition and the ability to perform ADL. INDENTITY and INDENTITY-2 are two RCT studies including more than 2,600 patients with mild-to-moderate AD from 31 countries with a treatment period of about 21 months. They compared effect of Semagacestat and placebo on measurements of ADAS-Cog and ADCS-ADL. In addition Semagacestat is associated with an increased risk of skin cancer. Clinical trial of LY450139 was thus halted.

#### *Passive immunization*

##### *Bapineuzumab*

Bapineuzumab is a monoclonal antibody which

binds to the N-terminal of A $\beta$  to enhance clearance of A $\beta$  from the brain. Bapineuzumab was injected intravenously into human bodies to act in a passive immunotherapy manner. A phase II RCT study which included 234 patients with mild to moderate AD, showed no significant advantage on cognitive and ADL functions after 78 weeks. In this trial, patients who did not carry Apo lipoprotein E4 (APOE4) alleles, performed better and had lower adverse effect (vascular edema) than the others<sup>(49)</sup>. This demonstrates the complicity of AD mechanism that both genetic and environmental factors play a role. Further investigation on the relationship between APOE4, A $\beta$ , and bapineuzumab should be done. Currently long-term phase II/III trials are now under investigation. Solanezumab is a humanized anti-A $\beta$  immunoglobulin G-1 monoclonal antibody. It has passed a phase II trial including 52 patients with mild to moderate AD which demonstrated increased A $\beta$  in plasma and CSF. However, there was no significant change in cognitive function or quantity of brain A $\beta$ . But there was no adverse effect such as brain inflammation revealed by MRI<sup>(50)</sup>. It will undergo two phase III RCT studies focusing on efficacy on cognition and ADL in patients with mild to moderate AD.

#### **Active immunization**

Active immunization uses A $\beta$  peptide or part of the peptide to induce anti-A $\beta$  antibody by human immune system to enhance clearance of A $\beta$  from the brain. This concept first succeeded in 1999 that Schenk et al, made PDAPP transgenic mice immunized with A $\beta$  showing decrease of amyloid plaque and neuritis<sup>(51)</sup>. AN-1792, a compound that A $\beta$  42 in combination with QS21 adjuvant was suddenly called off at a phase II trial in 2002, in which 15 participants developed symptomatic aseptic meningoencephalitis<sup>(52,53)</sup>. Nevertheless, this trial showed some definite pathological effect<sup>(53)</sup>. The adverse effect has a strong relationship with TGF-beta-1 induced T-cell toxicity<sup>(54)</sup>. Second generation active immunization vaccines have been under investigation since then. These vaccines used various fragments of A $\beta$  combined with promiscuous non-self T-cell epitope such as adenovirus vectors with A $\beta$  cDNA, or combined DNA epitope and

so on<sup>(55-57)</sup>. These second generation vaccines decrease insoluble A $\beta$  and amyloid plaque in the brain but not the soluble A $\beta$  and amyloid oligomers and have no effect on tauopathy<sup>(58-60)</sup>. As aforementioned, the patients receiving AN1792 (A $\beta$  42, a whole length A $\beta$ ) immunization showed greater ventricular enlargement as a percentage of baseline brain volume. Also greater hippocampal volume reduction was noted in patients on AN1792 than those patients on placebo. It is possible that volume change was due to amyloid removal or associated cerebral fluid shift. But the increased loss of brain volume was not reflected in cognitive improvement<sup>(61)</sup>. A phase-I study showed that immunization with AN1792 resulted in removal of amyloid plaque accumulated in cerebral cortex of those who received vaccine and died from AD. In a cohort analysis, there was no evidence of improved survival or prolongation of the time to severe dementia in the AN1792 group<sup>(62)</sup>. Furthermore, A $\beta$  was drained from the brain into intravascular space which might increase cerebrovascular A $\beta$  and precipitate cerebral amyloid angiopathy resulting in microvascular lesions or micro-hemorrhages after vaccination.

### ***Drugs blocking amyloid aggregation***

Tramiprosate (3-amino-1-propanesulfonic acid) is a glycosaminoglycan compound that binds to A $\beta$  monomers preventing formation of cytotoxic A $\beta$  oligomers thus enhancing A $\beta$  clearance from the brain. A phase II RCT study on patients with mild to moderate AD showed that A $\beta$  42 level in cerebral spinal fluid (CSF) was decreased in a dose-dependent manner<sup>(63)</sup>. However, the North American phase III RCT study on 1052 patient with mild to moderate AD failed to demonstrate a beneficial effect on the primary outcome, neither change in cognition or dementia staging after 18-month intervention. The negative result was considered to be from unexplained high inter-site variation. In spite tramiprosate was well tolerated.

### ***IVIG***

It was observed that the endogenous anti-amyloid antibody was slightly increased in CSF accompanied by impairment of blood brain barrier (BBB) which recruited

microglia and modulated complement-dependent amyloid phagocytosis both reducing amyloid burden. The amyloid plaque was decorated with IgG and phagocytic glia in non-immunized AD patients<sup>(64-66)</sup>. In the same vein, the administration of intravenous immunoglobulin, the passive immunotherapy, may be an effective approach. In a small-sample-sized clinical trial, IVIG was shown to decrease CSF A $\beta$ , to improve cognitive function and to stabilize cognitive function in AD patients during IVIG regimen<sup>(67)</sup>. Two Phase II RCT studies of IVIG on patients with mild to moderate AD are ongoing and one phase III trial evaluating safety and efficacy for IVIG is recruiting participants now.

### ***Strategies targeting Tau***

NFT and related tauopathy, composed of hyperphosphorylated tau protein, is a remarkable pathologic finding of AD. The underline mechanism was parallel and similar to A $\beta$ . Tau proteins are intra-neuron proteins, which bind to microtubules and stabilize microtubules for neuronal transport of vesicles to synapses. When tau is hyperphosphorylated, it is sequestered from microtubules and disrupts microtubule ensemble for vesicle transport, ultimately disturbs axonal function and reduces dendritic spines. Also hyperphosphorylated tau will self-aggregate, forming intermediate aggregates, paired helical filament and NFT. The intermediates aggregates, like A $\beta$  oligomers, are related to inflammation, oxidative cytotoxicity and neurodegeneration<sup>(68)</sup>. Since some phase III clinical trials based on the "amyloid hypothesis" showed negative results, we must target therapies for abnormal tau formation such as inhibition of tau hyperphosphorylation and tau aggregation.

Tau phosphorylation is regulated by kinase and phosphatase. It is believed that A $\beta$  induces hyperphosphorylated kinase cascade and will lead to tau phosphorylation. Thus to inhibit kinase or to enhance phosphatase may disturb the formation of abnormal tau. The major target kinases are GSK3 and cdk5/p25, whereas GSK3 plays a key role in AD neurodegeneration which also enhances A $\beta$  production<sup>(69)</sup>. Lithium not only can inhibit GSK3 but also can modulate neuron apoptosis<sup>(70)</sup>. It can decrease abnormal tau in vitro and in vivo; howev-

**Table 1.** Current treatment strategies under clinical trials and some completed studies\*

Mechanisms / Strategies		Treatments / Therapeutics	Trials / Status	
Anti-A $\beta$	↓ A $\beta$ production ( $\gamma$ -secretase inhibitor)	LY450139*	III	
		BMS-708163	II	
		NIC5-15*	II	
		GSI-953*	I	
	Anti- A $\beta$ aggregation	3APS (Alzhemed)	III	
		Metal-chelators:		
		8-OH-quinoline (PBT2)*	II	
	Neutralizing A $\beta$ toxicity and distribution (RAGE antagonist)	Syllo-inositol (ELND005)	II	
		PF0449470	II	
	↑ A $\beta$ clearance	Passive immunotherapy	TTP488	
			Bapinezumab (AAB-001)	III
			Solanezumab (LY2062430)	III
			PF-04360365	II
			MABT5102A	I
		IVIg	Active immunotherapy	
Octagam (10%)			II	
CAD106			II	
V950			I	
GSK-3 inhibitor			Lithium	II
↓ cytotoxicity	Anti-tau aggregation	Methylene blue (TRx0014)	II	
		Anti-oxidant		
	Anti-inflammatory	EGb761*	II / III / IV	
		Vitamin E	III	
		Curcumin, lutein*, soy isoflavone*	II	
		Etanercept, TNF- $\alpha$ antagonist	II	
		Cyclophosphamide*	I	
	Lipid metabolism regulation	HMG-CoA reductase*	II / III / IV	
		Omega-3 polyunsaturated fatty acid*	III / IV	
		Cholinergic stimulation		
↑ cognitive processing pathway	Cholinergic stimulation	Varenicline, RO5313534, ABT-126,	II	
		TC-1734		
		GSK 239512, ABT-288	II	
	Serotonin regulation	5-HT(6) antagonist SB-742457*,	II	
		SAM-531, Lu AE58054		
		5-HT(4) agonist: RRX-03140	II	
	Nerve growth factor Neurotrophic agents Restoring LTP (signal pathway modulators)	CERE-110 (AAV2-NGF)	II	
		T-817MA (cerebrolysin)	II	
		ST-101, PF-04447943	II	
Miscellaneous	↑ insulin utility	Insulin aspart*	II / IV	
		PPAR- $\alpha$ agonist: Rosiglitazone*	II / IV	
	Hormone regulation	SERM: Raloxifene	II	
	Vitamin B	Nicotimide	I / II	
	Antihistamine	Dimebolin*	III	

A $\beta$ : amyloid beta, RAGE: receptor for advanced glycation endproducts, GSK-3: Glycogen synthase kinase 3, LTP: long-term potentiation, NGF: nerve growth factor; Updated from <http://clinicaltrials.gov/ct2/> 2010/10/02.

er the benefit of lithium in neuroprotection and cognitive function remains controversial<sup>(71-72)</sup>. In patients with amnesic MCI, the effect of attenuating cognitive deficits and modification of biological markers are apparent in a phase II trial. There are other potent selective inhibitors of GSK-3 that showed promising results in preclinical models<sup>(73)</sup>.

Another promising compound is the methylthioninium chloride (MTC), so called methylene blue, with antioxidative ability through mitochondrial modulation that can reduce A $\beta$  oligomerization and can bind to the domain responding for tau aggregation<sup>(74-76)</sup>. In a preclinical study, it reverses the learning impairment in a cognitive deficit model<sup>(77)</sup>. A phase IIb RCT study of MTC monotherapy on patients with mild to moderate AD showed a significant improvement of cognitive function with long term benefit. It also showed that MTC can restore brain activity in brain tauopathy region<sup>(78)</sup>. These exciting results should be validated in a coming large-scale phase III clinical trial.

The main phosphatase of phosphorylated tau is PP2A and PP2B. PP2A is the major phosphatase down-regulated in Alzheimer's disease. Pin1, the peptidyl prolyl cis/trans isomerase can facilitate dephosphorylation of phosphatase. It can be activated by A $\beta$ - oligomers-induced tau-phosphorylation, and can modulate APP 79-81<sup>(78)</sup>. The possibility of regulating this tau-related molecule may develop into new therapeutics.

Vaccines consist of phosphor-tau epitope can reduce aggregated tau in the brain and can prevent or slow down progression of the tangle-related behavioral and cognitive impairment in animal models<sup>(82)</sup>.

### ***Dimebolin (latreperidine)***

Dimebolin, so called dimebon, is a retired Russian anti-histamine drug. It was found that it can improve learning in Alzheimer's animal models<sup>(83,84)</sup>. Dimebolin was reported to inhibit acetyl cholinesterase, to potentiate activities of AMPA receptors and to block NMDA receptors<sup>(85)</sup>. It also can enhance mitochondrial function<sup>(86)</sup>, or be neuroprotective by selectively blocking L-type Ca<sup>2+</sup> channels, by inhibiting A $\beta$ -dependent calcium influx into neurons<sup>(87)</sup>, and by antagonizing 5-HT(6)

receptors with high affinity<sup>(88)</sup>. All suggest that dimebolin may play a role in enhancing cognition in preclinical models and in clinic trials.

A phase II RCT study enrolled 183 patients with mild-to-moderate AD showed significant benefit in cognitive function after 26-week dimebolin treatment<sup>(89)</sup>. However, a recent phase III study, CONNECTION, showed negative results of dimebolin<sup>(90)</sup>. In this multinational RCT study recruiting 598 patients with mild-to-moderate AD, no significant difference was achieved on cognitive function, ADL, behaviors and global functions at week 26. Dimebolin was generally well tolerated, but one study indicated the acute admission of dimebolin may elevate extracellular A $\beta$  both in vitro and in vivo<sup>(91)</sup>.

### ***EGb761 (Ginkgo Biloba)***

EGb761 was known to have antioxidant and free radical-scavenging activities. Theoretically it could reduce A $\beta$  related reactive oxygen species (ROS) induced apoptosis. It may increase APP's releasing of the non-amyloidogenic metabolites through regulation of the  $\alpha$ -secretase pathways<sup>(92)</sup>. It also may stimulate neurogenesis enhancing the learning and memory capacities; and may lower the APP level in AD transgenic mice<sup>(93-95)</sup>. However, a systemic review of 36 RCT studies on patients with cognitive impairment, dementia, and AD concluded that the benefit and efficacy were inconsistent<sup>(96)</sup>.

### ***Vitamin E***

The transgenic mice with Vitamin E deprivation showed elevated APP and increased lipid peroxidation causing impaired A $\beta$  clearance and early cognitive dys 97,98<sup>(78)</sup>. Thus Vitamin E, a potent anti-oxidant, may play a role in the prevention and treatment of AD<sup>(99)</sup>. Epidemiologic studies suggested that dietary intake of vitamin E reduced the risk of AD. A review concluded fewer moderately to severe AD patients taking Vitamin E reached the incapacity over a two-year period<sup>(100)</sup>. An RCT study demonstrated that among all patients receiving Vitamin E, only those with reduced blood oxidized glutathione maintained MMSE scores but those with non-reduced glutathione showed cognitive decline to

levels even lower than those who taking placebo<sup>(101)</sup>.

### **Statins**

APOE is a cholesterol carrier in CNS and APOE4 may aggravate A $\beta$  deposition and tau hyperphosphorylation. Carrying APOE4 allele is a significant risk factor for sporadic AD. Epidemiological study showed that people with a higher cholesterol level had a higher risk of developing AD. In animal studies, lowering cholesterol level may slow down the expression of Alzheimer's pathology, reduce NFT and amyloid burden, and reverse learning and memory<sup>(102-104)</sup>. A cohort study suggested that elective statin use can significantly reduce risk of AD in individuals taking anti-inflammatory agents<sup>(105)</sup>. But review of RCT studies of statin revealed decreasing cholesterol level without reducing risk of AD or dementia<sup>(106)</sup>. An RCT study (LEADe) of atorvastatin 80 mg/day for 72 weeks on 640 patients with mild to moderate AD showed no effect on cognitive or global function<sup>(107)</sup>.

### **DHA (docosahexaenoic acid)**

DHA is an omega-3 polyunsaturated fatty acyl chain concentrated in phospholipids of brain and retina. It can attenuate A $\beta$  secretion and enhance synthesis of the neuroprotectin (NDP1), which can repress inflammation, oxidative stress, and cell apoptosis induced by A $\beta$  42 and promote neuronal survival. DHA and NDP1 were reduced in AD patients<sup>(108)</sup>. In animal models, DHA presented a beneficial effect on decreasing AD pathology, cognitive impairment, synaptic dysfunction, and tau hyperphosphorylation<sup>(109)</sup>. Animals on DHA depletion diet showed learning and memory impairment; increased inflammatory and oxidative damage to neurons and synapses in the brain<sup>(110)</sup>. Epidemiological studies showed conflicting results between fish intake, DHA blood level and the incidence of AD<sup>(111,112)</sup>. A systemic review showed no evidence that dietary or supplemental omega-3 polyunsaturated fatty acid could reduce risk of cognitive impairment or dementia in healthy elderly<sup>(113)</sup>.

### **Scyllo-inositol**

Scyllo-inositol can directly bind to A $\beta$  oligomers and restore LPT of neurons and synaptic plasticity in

hippocampus. In preclinical trials, scyllo-inositol can penetrate BBB, and can reduce insoluble A $\beta$ 40, A $\beta$ 42, and amyloid plaque in the brain, and can improve performance of learning<sup>(114,115)</sup>. Now oral ELND005 is under a phase II clinical trial evaluating safety and efficacy for mild to moderate AD patients.

### **RAGE-antagonist**

Receptors for advanced glycation end products (RAGE) is a molecule of immunoglobulin superfamily localized in neurons, microglia, astrocytes and BBB. RAGE enhanced in AD can help transport A $\beta$  from vascular circulation to the brain. A $\beta$  binding to RAGE interferes with synaptic LPT resulting in neuronal stress, cytotoxicity, inflammation and consequent memory and learning deficits. RAGE enhances generation and accumulation of the A $\beta$  in CNS by modulating BACE1 which accounts for the role of type II DM as a risk of AD<sup>(116-119)</sup>. Soluble RAGE can bind to systemic A $\beta$  decreasing accumulation of the brain A $\beta$  and improving learning and memory of transgenic mice. The effort on RAGE proteolysis as a therapeutic target for AD has been carried on<sup>(120)</sup>. PF04494700, an RAGE antagonist, is currently under evaluation for AD treatment in a phase II trial.

### **Nerve Growth Factor**

The cholinergic neuron loss in basal forebrain has a strong correlation with the severity of AD. Through in vitro and in vivo experiments, nerve growth factors (NGF) showed effect of neuronal protection, augmenting cholinergic function by enhancing choline acetyltransferase, and facilitating differentiation of neuron progenitor cell to cholinergic type. Induction function of the NGF signaling is decreased in an elder rat model<sup>(121)</sup>. Furthermore, over expression of pro-NGF, attenuated maturation of NGF, and enhanced degradation of mature NGF deprive cholinergic neurons and increase A $\beta$  production through switching the APP metabolic pathway<sup>(122)</sup>. On the other hand increased APP will interfere with the function of NGF and is detrimental to cholinergic neurons<sup>(123)</sup>. Scientists have been successful in using NGF or recombinants of NGF in AD animal models,



which showed reversal of cholinergic neurons, and improvement of learning and memory through either intranasal administration or implantation<sup>(124-126)</sup>.

In early clinical trials, molecules enhancing neurogenesis with neuroprotective abilities, like AIT-082 (neotrofin) or SR57667B (paliroden), were arrested at phase-I trials. The first genetic approach is an open label study, including 8 patients with mild AD, receiving autologous genetically modified NGF-producing fibroblasts into basal forebrain. After 22 months, the rate of cognitive decline was slowed down with increased metabolic activity in the cortical areas of PET scan<sup>(127)</sup>.

Recently virus vector loaded with NGF gene or mRNA, implanted into brain parenchyma of animals of AD model, brought exciting results<sup>(128,129)</sup>. These results lead to phase I and II studies on the CERE-110 (AVV2-NGF), an adeno-associated viral gene delivery vector that encodes human NGF. The CERE-110 delivered to human nucleus basalis of Meynert through stereotactic surgery, is currently assessed for safety, tolerability and biologic activity for a minimum of two-year period.

### **Miscellaneous**

#### **Serotonin regulation**

Recently the association between serotonin and neurodegenerative diseases is noticed. Pathology and image studies of AD patients showed that 5-HT<sub>1</sub> receptors were increased in MCI stage but were decreased when progressing to AD. The reduction was associated with the severity of dementia. Studies showed that 5-HT<sub>1</sub> antagonist could activate neuronal cycle to improve cognitive function<sup>(130,131)</sup>. The 5-HT<sub>1</sub> antagonist, xaliproden has been under clinical trial which showed disappointing results<sup>(132)</sup>. 5-HT<sub>6</sub> antagonist enhanced cholinergic transmission, improved learning and memory; probably augmented monoaminergic transmission both in vivo and in vitro<sup>(133-134)</sup>. Some of these antagonists (e.g., SB-742456) are now under phase II trials. The 5-HT<sub>4</sub> agonist can modulate release of acetylcholine through activating cAMP pathway and can promote  $\alpha$ -amyloid and reduce A $\beta$  production<sup>(135,136)</sup>. RRX-03140, a 5-HT<sub>4</sub> agonist, is in a phase II trial combined with donepezil.

#### **Insulin metabolism**

Impaired insulin pathway shows reduced protection of synaptic plasticity damaged by A $\beta$  accumulation and by over-activation of GSK3 which could lead to tau hyperphosphorylation and NFT formation<sup>(137)</sup>. The central resistance may be a result of chronic hyperinsulinemia, hyperglycemia, and peripheral resistance in type II diabetes mellitus (DM). Hyperinsulinemia causes increased amyloid deposition which is modulated by insulin-degrading enzyme. Hyperglycemia can induce advanced glycation end product and oxidative stress critical for AD progression<sup>(138,139)</sup>. In an opposite way, A $\beta$  peptide binding to synapse interferes with normal insulin signaling pathway and cognitive function<sup>(140)</sup>. In a short summary, to enhance insulin utilization, to increase CNS insulin or to sensitize insulin receptor may provide a chance for AD treatment. One study included patients with mild to moderate AD and DM showed that oral anti-diabetic drugs combined with insulin can slow down cognitive decline and can maintain global function better than those under oral anti-diabetic monotherapy in an one-year period<sup>(141)</sup>. A phase II study evaluating the efficacy of insulin on cognitive function of patients with mild AD utilizing functional MRI is ongoing. Rosiglitazone is an  $\alpha$ -peroxisome proliferator-activated receptors (PPAR- $\alpha$ ) agonist, which can enhance insulin sensitivity. In recent clinical trials, it was showed to bring cognitive and functional improvement for AD patients. But the APOE4 alle carriers did not gain benefit from rosiglitazone<sup>(142,143)</sup>.

#### **Restoring long-term potentiation and synaptic plasticity**

A $\beta$  oligomers can cause impairment of LTP and synaptic plasticity. Thus enhancing LTP and synaptic plasticity by modulating associated molecules may be promising in the future<sup>(144)</sup>. A $\beta$  oligomers can disturb phosphorylation of the calcium-calmodulin dependent protein kinase 2 (CaMK II), which is an important molecule for expression of LTP. ZSET1446 (ST-101) can stimulate CaMK II and protein kinase C (PKC) which cognitive-enhancing effect was proved in an animal study<sup>(145)</sup>. Other pathways contribute to synaptic plasticity

ty, like NO /cGMP /cGK /CREB cascade also could be interrupted by A $\beta$ <sup>(146)</sup>. Thus, enhancing cGMP phosphorylation by inhibiting phosphodiesterase (PDE) may enforce the synaptic plasticity. A PDE9A inhibitor, PF-04447943, was shown to increase cGMP in human CSF<sup>(147)</sup>. The efficacy on cognitive, behavioral and overall symptoms of AD is currently under investigation by a phase II trial.

### ***Histamine antagonist***

The H3 receptors were preserved in the brains of AD patients comparable to normal controls; and the binding density showed positive correlation with disease severity. Endogenous histamine interacting with H3 receptor decreases release of other neurotransmitters such as dopamine and serotonin, which are closely related to cognitive processing pathway<sup>(148,149)</sup>. GSK189254, an H3 antagonist, increases release of dopamine in the anterior cingulate cortex and acetylcholine in the dorsal hippocampus, which correlates with an improved performance of rats in diverse cognition assessments<sup>(150)</sup>. It is now under a phase II trial to evaluate its safety and efficacy.

### ***Neurotrophic agents***

A neurotrophic agent is a compound capable of neuroprotection, restoring neuroplasticity, improving neuronal survival, or even promoting neurogenesis, thus considered a therapy for AD. Among these agents, cerybrolisin, a peptide acting like endogenous neurotrophin was demonstrated to improve global function in clinical trials through intravenous route administration<sup>(151,152)</sup>. Another promising drug is the T-817MA, which can fight against A $\beta$  induced toxicity; and it can ameliorate cognitive deficits in animal models<sup>(153,154)</sup>. A phase II clinical trial is under preparation.

Until now there is still no single treatment that can successfully stop or reverse the progression of AD. We propose that in the near future therapeutics of various combination of symptomatic treatments (AChEI and memantine) and disease modifying therapies (e.g., vaccines targeting A $\beta$  and/ or tau protein,  $\gamma$ -secretase)<sup>(36-39,42,155-157)</sup> will emerge as the standard regimen of AD

treatment which should be able to provide a much better treatment efficacy than all current approaches.

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