

## Advances in Drug Therapy for Alzheimer's Disease\*

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**Summary:** Alzheimer's disease (AD) is a chronic neurodegenerative disease that mainly causes dementia. It is a serious threat to the health of the global elderly population. Considerable money and effort has been invested in the development of drug therapy for AD worldwide. Many drug therapies are currently under development or in clinical trials, based on two known mechanisms of AD, namely, A $\beta$  toxicity and the abnormal Tau hyperphosphorylation. Numerous drugs are also being developed for other AD associated mechanisms such as neuroinflammation, neurotransmitter imbalance, oxidative damage and mitochondrial dysfunction, neuron loss and degeneration. Even so, the number of drugs that can successfully improve symptoms or delay the progression of the disease remains very limited. However, multi-drug combinations may provide a new avenue for drug therapy for AD. In addition, early diagnosis of AD and timely initiation of treatment may allow drugs that act on the early pathological processes of AD to help improve the symptoms and prevent the progression of the condition.

**Key words:** Alzheimer's disease; A $\beta$ ; tau; drug therapy

Alzheimer's disease (AD) is a neurodegenerative disease that mainly affects the elderly over 60 years old. Intracellular neurofibrillary tangles (NFTs) associated with tau lesions and extracellular senile plaques (SP) associated with A $\beta$  toxicity are the two major neuropathological features of AD<sup>[1]</sup>. It is estimated that there are about 44 million AD patients in the world, and with the aging of the population, the number will more than double by 2050<sup>[2]</sup>. At present, there are only 6 drugs approved by FDA for AD treatment, including 4 kinds of acetylcholinesterase inhibitors (ACEIs): tacrine, donepezil, galantamine, rivastigmine, and a NMDA receptor blocker memantine, and an orexin receptor antagonist Suvorexant (Belsomra, MK-4305, <https://www.alzforum.org/therapeutics/suvorexantrevised>), which are all symptom modifying drugs<sup>[3, 4]</sup>. So far, no drug for disease modifying treatment (DMT) has

been approved to enter the market, although a large number of funds and manpower have been invested in the research and development of DMT drugs. As of February 27, 2020, according to the ClinicalTrials.gov, there are 97 DMT drugs in clinical trials<sup>[5]</sup>. In view of the urgent need of drugs for the treatment of AD, here, we review the progress of drug therapies for AD related to tau lesions and A $\beta$  toxicity, and other AD pathological changes.

### 1 DRUG THERAPY BASED ON KEY MOLECULAR TARGETS OF A $\beta$ TOXIC PATHWAY

Amyloid beta (A $\beta$ ) is mainly formed by the cleavage of amyloid precursor protein (APP). The cleavage of APP by  $\beta$ -secretase and  $\gamma$ -secretase mainly produces A $\beta$  1-40 and A $\beta$  1-42, while the cleavage by  $\beta$ -secretase and  $\alpha$ -secretase or  $\alpha$ -secretase and  $\gamma$ -secretase mainly produces A $\beta$  1-14, A $\beta$  1-15, A $\beta$  1-16 or P3 (A $\beta$  17-40/42)<sup>[6]</sup>. A $\beta$  1-40 and A $\beta$  1-42 are easy to aggregate and deposit and are the main components of SP, while A $\beta$  1-14, A $\beta$  1-15, A $\beta$  1-16 and P3 are not easy to deposit and can be effectively removed in time<sup>[7]</sup>. The production and deposition of A $\beta$  are thought to be the initiating factors of AD pathological changes, leading to subsequent lesions, such as NFTs, neuron loss, vascular injury, dementia, etc<sup>[8]</sup>. It is

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generally believed that A $\beta$  plays an important role in the occurrence and development of AD. Therefore, reducing A $\beta$  deposition will help to alleviate AD and improve AD related cognitive impairment. At present, the drug research and development strategies targeting A $\beta$ -related pathological mechanisms mainly include: (1) inhibition of  $\beta$ -secretase; (2) inhibition of  $\gamma$ -secretase; (3) promotion of  $\alpha$ -secretase; (4) reduction of APP production; (5) promotion of A $\beta$  clearance (fig. 1).

Cytotoxic A $\beta$  1-40 and A $\beta$  1-42 results from the successive cleavage of APP by  $\beta$ -secretase and  $\gamma$ -secretase, and deposit to form SP, which will eventually lead to pathological changes and symptoms of AD. APP can also produce nontoxic A $\beta$  1-14/15/16 or P3 (A $\beta$  17-40/42) after cleavage by  $\beta$ -secretase and  $\alpha$ -secretase or  $\alpha$ -secretase and  $\gamma$ -secretase respectively. These metabolites are not easy to deposit and can be effectively removed. Therefore, up-regulating  $\alpha$ -secretase, inhibiting  $\beta$ -secretase and  $\gamma$ -secretase, as well as reducing APP production and promoting A $\beta$  clearance are the main strategies for AD drug research and development aiming at A $\beta$  toxicity.

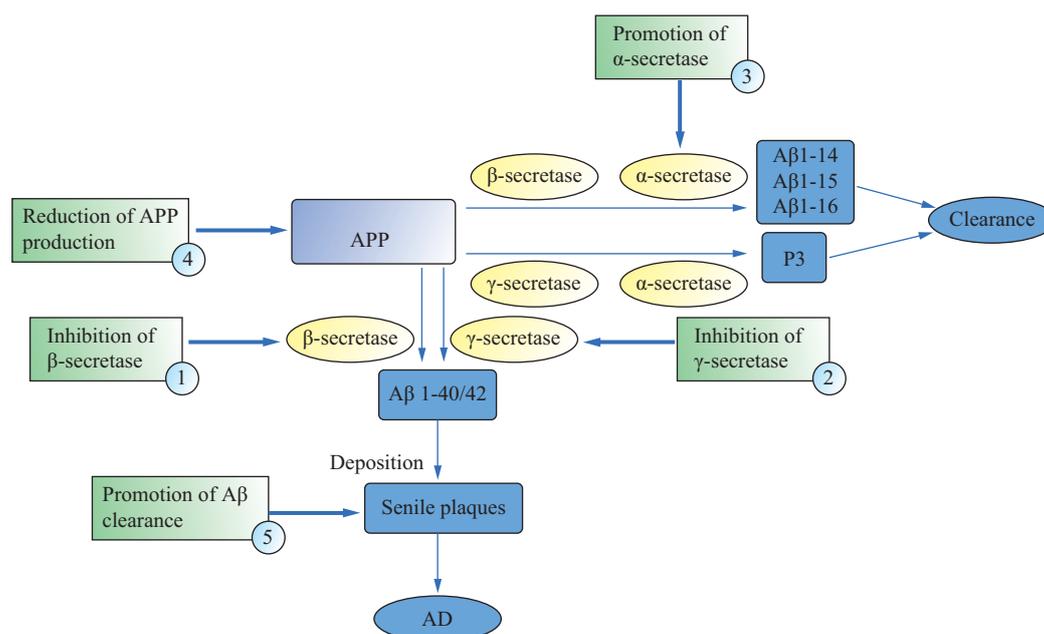
### 1.1 Inhibition of $\beta$ -Secretase

$\beta$ -secretase, also known as  $\beta$ -site amyloid precursor protein cleaving enzyme 1 (BACE1), is the A $\beta$  production rate limiting enzyme. BACE1 can promote APP cleavage to produce A $\beta$ , and thus preventing this process may reduce not only the production but also the subsequent deposition of A $\beta$ . Therefore, inhibition of BACE1 is one of the main directions of AD drug development<sup>[9]</sup>. However, five BACE1 inhibitors

elenbecestat, umibecestat, lanabecestat, atabecestat and verubecestat all failed clinical trials due to the safety or effectiveness problems<sup>[10]</sup>. The result has left many people, who have expectations and hope for BACE1 inhibitors, disappointed. However, the BACE1 inhibitor CNP520, which reduces the level of A $\beta$  in cerebrospinal fluid (CSF) and the formation of A $\beta$  plaques in experimental animal brains, also shows promises in humans. In healthy adults over 60 years old, CNP520 can reduce the level of A $\beta$  in CSF in a dose-dependent manner, and has good safety and tolerance. It is expected to be used for AD prevention<sup>[11]</sup>. BACE2, a homologue of BACE1, encoded by a gene on chromosome 21 is also involved in AD pathogenesis but with an anti-amyloidogenic effect in opposition to BACE1. BACE2 can generate a 1–19 fragment by cleaving APP  $\beta$ -CTF (product of  $\beta$ -secretase)<sup>[12–14]</sup>, and thus could prevent the formation of A $\beta$ . Moreover, in acidic condition (pH 3.5–4), BACE2 can rapidly and effectively degrade synthetic A $\beta$ 40/42 peptides by cutting after aa20 and aa34, to generate the 1–20 and 1–34 products<sup>[12, 15]</sup>. Interestingly, BACE2 was recently reported to be cross-inhibited by clinically trialed BACE1 inhibitors LY2886721 and  $\beta$ -secretase inhibitor IV<sup>[16]</sup>. This might at least in part explain the failure of BACE1 inhibition therapy. Perhaps, BACE1 inhibition could be a more feasible treatment method to prevent and reverse early AD, but cross-inhibition of homologue proteins like BACE2 should be taken in consideration.

### 1.2 Inhibition of $\gamma$ -Secretase

Inhibition of  $\gamma$ -secretase is considered to reduce



**Fig. 1** AD drug development strategy for A $\beta$  metabolism

Based on the A $\beta$ -related pathological alterations, the drug research and development strategies mainly include: (1) inhibition of  $\beta$ -secretase; (2) inhibition of  $\gamma$ -secretase; (3) promotion of  $\alpha$ -secretase; (4) reduction of APP production; (5) promotion of A $\beta$  clearance

the production of A $\beta$ , thus improving the pathological changes and symptoms of AD associated with A $\beta$  toxicity<sup>[17]</sup>. This led to the development of many  $\gamma$ -secretase inhibitors. Semagacestat, one of the  $\gamma$ -secretase inhibitors, successfully reduces the levels of A $\beta$  in CSF and brain in animal experiments, and in the CSF of humans<sup>[18]</sup>. However, in a phase 3 clinical trial, Semagacestat did not improve the cognitive level of AD patients compared with placebo group, and patients receiving large dose of drug had serious deterioration of physical function, increased risk of adverse reactions such as skin cancer and infection, resulting in pre-term termination of the trial<sup>[19]</sup>. Avagacestat, another  $\gamma$ -secretase inhibitor, has also been proved to have no significant improvement effect in clinical trials, and has serious adverse reactions at high dose<sup>[20]</sup>. At present, the safety and efficacy of inhibition of  $\gamma$ -secretase need further verification.

### 1.3 Promotion of $\alpha$ -Secretase

Another major enzyme involved in APP processing is  $\alpha$ -secretase. APP is truncated by  $\alpha$ -secretase to produce a soluble N-terminal domain of APP (sAPP $\alpha$ ). In addition, APP can be cut by  $\beta$ -secretase and  $\alpha$ -secretase in sequence to produce A $\beta$  1–14/15/16, which is not neurotoxic. Therefore, enhancing  $\alpha$ -secretase activity may help to improve AD<sup>[21]</sup>. Etazolate, a selective GABAA receptor agonist, has been shown to have a dose-dependent protective effect on rat cortical neurons from A $\beta$ -induced toxicity. The results showed that Etazolate stimulated GABAA receptor and enhanced the pathway of  $\alpha$ -secretase enzyme shear, which promoted the production of sAPP $\alpha$  in rat cortical neurons and guinea pig brains, and thus played a neuroprotective role<sup>[22]</sup>. At present, there are two kinds of  $\alpha$ -secretase enzyme enhancers (APH1105 and ID1201) in clinical trials. The awaiting results will shed light on the effectiveness and efficacy of the promotion of  $\alpha$ -secretase activity in AD therapeutics.

### 1.4 Reduction of APP Production

Since neurotoxic A $\beta$  is produced by the cleavage of APP, reducing the production of APP itself has become an idea for the treatment of AD. Previous studies have revealed that the drug Posiphen can reduce the levels of APP and A $\beta$  in human neuroblastoma cells by inhibiting the synthesis of APP, which also produces the same effect in mice<sup>[23]</sup>. A recent study showed that Posiphen improved the cognitive, memory and synaptic functions of APP/PS-1 mice (a common AD mouse model) by reducing APP production at the transcriptional level, and did not affect the visual sensitivity and motor function of AD mice, nor did it have adverse effects on normal control mice<sup>[24]</sup>. At present, the phase 2 clinical trial of Posiphen in the treatment of AD is in the recruitment stage<sup>[25]</sup>.

### 1.5 Promotion of A $\beta$ Clearance

The imbalance between A $\beta$  production and

clearance is considered to be the promoter of A $\beta$  aggregation and deposition, and thus AD<sup>[26]</sup>. The metabolic marker method was used to confirm that the clearance rates of A $\beta$  1-40 and A $\beta$  1-42 in patients with AD were lower than those in normal people, but there was no difference in the generation rate, indicating that the impaired clearance rate of A $\beta$  is one of the characteristics of AD<sup>[27]</sup>. The treatment of AD aiming at promoting the clearance of A $\beta$  is evolving rapidly, leading to the development of therapies like monoclonal antibodies, A $\beta$  vaccine, plasma exchange and albumin replacement therapy among others.

Monoclonal antibodies targeting A $\beta$  monomers, oligomers and SPs are the main drugs used to promote A $\beta$  clearance. The monoclonal antibody Aducanumab is shown to effectively bind A $\beta$  in transgenic AD mouse model and reduce soluble and insoluble A $\beta$  in a dose-dependent manner; while in prodromal or mild AD patients, intravenous injection of Aducanumab was also found to reduce A $\beta$ <sup>[28]</sup>. Unfortunately, a recent phase 3 clinical trial of Aducanumab in patients with mild AD did not significantly improve cognitive impairment<sup>[29]</sup>. This failure was speculated to be due to the fact that the pathological changes of the recruited AD patients at the beginning of the trial are so severe that Aducanumab cannot reverse them<sup>[29]</sup>. This indicates that Aducanumab is not completely inefficient for AD treatment, but rather the stage of the disease might be important in the patient selection for Aducanumab therapy. Another monoclonal antibody that is holding promises is Crenezumab. This antibody can bind to oligomeric A $\beta$  and fibrillar A $\beta$  with high affinity, and is currently in phase 3 clinical trials<sup>[30]</sup>. Other monoclonal antibodies including Bapineuzumab, Solanezumab and Gantenerumab were found to be ineffective in phase 3 clinical trials<sup>[31–33]</sup>. It is generally believed that A $\beta$  is an early promoter of the pathological process of AD, and we know that DMT drug therapy for chronic diseases should be started at the beginning or at least at an early stage of pathophysiological process. Therefore, monoclonal antibody therapy aiming to promote A $\beta$  clearance may be more suitable for preventive or early disease treatment. Thus, patient selection is of important use for a better outcome. Crenezumab has been used to prevent autosomal dominant AD<sup>[34]</sup>.

Other drug therapies to clear A $\beta$  are also under development. Plasma exchange and albumin replacement therapy have been proved to be effective in improving the cognitive and brain function of AD patients<sup>[35]</sup>. The vaccine CAD106 successfully induces effective A $\beta$  antibody in APP transgenic mice, thus reducing A $\beta$  deposition in mouse brain, and it does not show obvious inflammatory reactions<sup>[36]</sup>. The response rate of the vaccine UB-311 reached 100% in phase 1 clinical trial, and has entered phase 2 clinical trial<sup>[25, 37]</sup>. Intravenous immunoglobulin (IVIG) is also considered

for the treatment of AD, because IVIG contains natural A $\beta$  autoantibodies (nabs-A $\beta$ ), which can specifically bind neurotoxic A $\beta$ <sup>[38]</sup>. In support of this is the fact that these nabs-A $\beta$  were found to be decreased in AD patients in comparison with healthy controls<sup>[39]</sup>. Moreover, fluorodeoxyglucose (FDG)-positron emission tomography (PET) shows that the glucose metabolism of IVIG group is significantly improved compared with the control group, indicating that IVIG has beneficial effect on AD patients<sup>[40]</sup>. IVIG treatment of AD needs further exploration and delicate interpretation of current results. Other A $\beta$  scavenging agents such as Thiethylperazine (antiemetic; activated transporter ABCC1) and Efavirenz (non-nucleoside reverse transcriptase inhibitor) are also in clinical trials<sup>[25]</sup>.

## 2 DRUG THERAPY FOR ABNORMAL HYPERPHOSPHORYLATION OF TAU

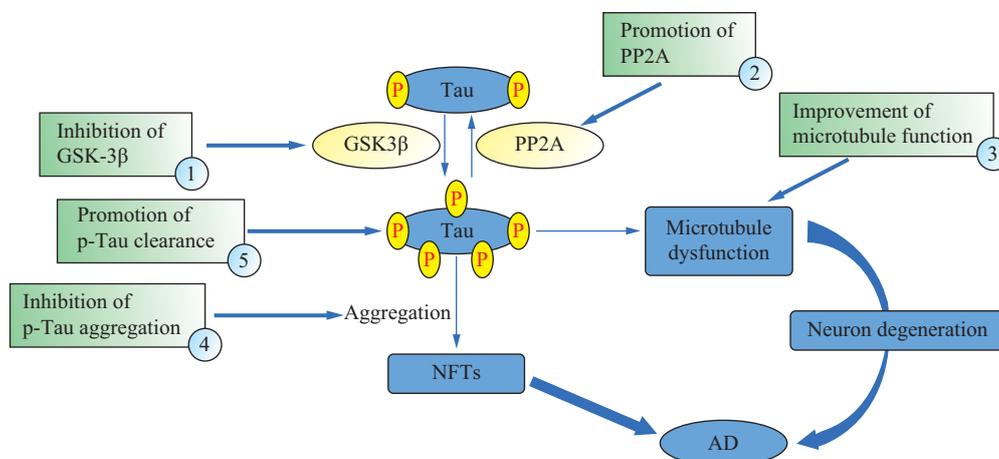
Tau is a microtubule binding protein. Normal Tau promotes the assembly of microtubules. However, hyperphosphorylated Tau will cause the disruption of microtubules<sup>[41]</sup>. Abnormal hyperphosphorylation of tau protein in the brain of AD patients promotes the formation and accumulation of NFTs. The increased protein kinase activity or decreased phosphatase activity is the direct cause of tau protein hyperphosphorylation. Glycogen synthase kinase 3  $\beta$  (GSK-3 $\beta$ ) and protein phosphatase 2A (PP2A) are important tau related kinases and phosphatase<sup>[42]</sup>. NFTs formed by hyperphosphorylated tau (p-tau) accumulation are the main cause of cognitive dysfunction and dementia in AD patients. P-tau can interfere with the assembly and depolymerization of microtubules, resulting in the imbalance of microtubule dynamics, and then affect the transport of neuronal axons and dendrites, leading to

neuronal degeneration and promoting the development of AD<sup>[43-45]</sup>. Therefore, reducing tau protein hyperphosphorylation and p-tau aggregation will help to improve AD. Drug development strategies to reduce abnormal hyperphosphorylation of tau include: (1) inhibition of GSK-3 $\beta$  activity; (2) promotion of PP2A activity; (3) improvement of microtubule function; (4) inhibition of p-tau aggregation; (5) promotion of P-tau clearance (fig. 2).

Tau protein is phosphorylated by GSK-3 $\beta$  to form p-tau, and p-tau is reduced to normal tau protein by PP2A dephosphorylation. P-tau is prone to aggregate and form NFTs, and finally progresses to AD. On the other hand, p-tau leads to microtubule dynamics imbalance, abnormal function, disassembly and then leads to neurodegenerative changes, which contributes to the pathological process of AD. So, inhibition of GSK-3 $\beta$ , enhancement of PP2A activities, improvement of microtubule function, inhibition of p-tau aggregation and promotion of p-tau clearance are the main drug research directions for tau lesions.

### 2.1 Inhibition of GSK-3 $\beta$

GSK-3 $\beta$  is an important and main tau related protein kinase. Many studies have reported an increased activity of GSK-3 $\beta$  in AD animal models and AD patients' brain. The upregulated activity of GSK-3 $\beta$  is the main cause of hyperphosphorylation of tau and is a key event in the formation of NFTs. Additionally, GSK-3 $\beta$  may also be related to APP processing, A $\beta$  production, neuronal apoptosis, and learning and memory deficits<sup>[46]</sup>. Therefore, inhibiting or at least decreasing the activity of GSK-3 $\beta$  is an option in the quest of AD therapy. Lithium has been proved to inhibit GSK-3 $\beta$  activity. In transgenic AD mice model, lithium ion reduces tau protein phosphorylation and A $\beta$  production, and improves spatial learning and memory ability<sup>[47]</sup>. Recently, the use of "micro dose" lithium ion



**Fig. 2** Pathological mechanism of tau protein and corresponding AD drug development strategy

Tau hyperphosphorylation is due to protein kinases/protein phosphatases imbalance. Glycogen synthase kinase 3  $\beta$  (GSK-3 $\beta$ ) and protein phosphatase 2A (PP2A) are important tau related kinase and phosphatase. Based on the reduction of tau hyperphosphorylation, AD drug development strategies mainly include: (1) inhibition of GSK-3 $\beta$  activity; (2) promotion of PP2A activity; (3) improvement of microtubule function; (4) inhibition of p-tau aggregation; (5) promotion of p-tau clearance

in the treatment of mild cognitive impairment (MCI) has achieved initial results, and further long-term trials are needed to confirm the efficacy and safety of lithium ion<sup>[48]</sup>. ANAVEX 2-73, a synthetic sigma-1 receptor agonist and GSK-3 $\beta$  inhibitor, was reported to improve cognition and reduce tau protein phosphorylation, and is currently in phase 2 clinical trial<sup>[25]</sup>.

## 2.2 Promotion of PP2A

Compared with protein phosphatase 2B (PP2B) and protein phosphatase-1 (PP-1), the dephosphorylation activity of tau protein by PP2A is the strongest<sup>[42]</sup>. PP2A accounts for about 70% of tau dephosphorylation. This suggests that enhancement of PP2A activity may be a potential therapeutic strategy for AD. Sodium selenate has been proved to reduce tau protein phosphorylation by enhancing PP2A activity. In two independent tau pathological transgenic mice strains, sodium selenate effectively reduced tau protein hyperphosphorylation and completely eliminated the formation of NFTs. In addition, sodium selenate also improved the conditional memory and motor function of mice<sup>[49]</sup>. Phase 2 clinical trial showed that sodium selenate has good safety and tolerance<sup>[50]</sup>, and it is expected to become a drug for AD treatment. Memantine, another drug approved by FDA to improve symptoms of AD, used to play a role in antagonizing NMDA receptor. Now it has been confirmed that memantine can activate PP2A by inhibiting PP2A inhibitor 2 (I2PP2A) *in vitro*, thus reducing tau protein hyperphosphorylation<sup>[51]</sup>. This suggests that memantine may also have the effect of reversing tau pathology and can be used for disease remission therapy (DMT).

## 2.3 Improvement of Microtubule Function

Tau protein is hyperphosphorylated in the brain of AD patients, resulting in defects in the process of tubulin assembly into microtubules<sup>[52]</sup>. The defect of microtubule dynamics leads to neuron degeneration and promotes the occurrence and development of AD. The microtubule was thus seen as a therapeutic target and microtubule stabilizers were synthesized and evaluated for AD therapy. For example, TPI-287, a microtubule stabilizer that can easily cross the blood-brain barrier with higher concentration in the brain than blood, was reported to reduce brain levels of hyperphosphorylated tau and improve Morris Water Maze performance in PS19 tau-transgenic mice<sup>[53]</sup>. TPI-287 was tried in humans and it was intravenously injected into patients with mild to moderate AD in a phase 1/2 clinical trial, unfortunately the results showed that the drug was not well tolerated by patients as severe hypersensitivity reactions were observed<sup>[54]</sup>.

## 2.4 Inhibition of P-Tau Aggregation

Tau protein has the capacity to form toxic oligomers that are resistant to proteolysis thus forming tau aggregates into NFTs. These tau aggregates have the capacity to seed and propagate the pathology to other

regions. Inhibition of p-tau aggregation to form NFTs may help to improve the pathological changes of AD, so p-tau aggregation inhibitor is expected to become one of the DMT drugs. Methylene blue, a phenothiazine derivative, can inhibit the aggregation of p-tau. It is found that it helps to improve cognitive dysfunction in APP/PS1 transgenic mice, and this improvement is effective before and after the occurrence of A $\beta$  lesions, indicating that methylene blue could be beneficial in the prevention and treatment of AD<sup>[55]</sup>. A phase 2 clinical trial with methylene blue in the treatment of mild to moderate AD showed that the cognitive function of patients with moderate AD was improved after 24 weeks of treatment with methylene blue, and after 50 weeks of continuous treatment for both mild and moderate AD patients<sup>[55]</sup>. At present, methylene blue is in further clinical trials<sup>[25]</sup>.

## 2.5 Promotion of P-Tau Clearance

Tau lesions are better correlated with the degree of dementia than A $\beta$  lesions, therefore the clearance of aggregated p-tau may be more effective when AD cognitive impairment is significant<sup>[56]</sup>. At present, immunotherapy is the main strategy used to promote p-tau clearance, and includes active immunity (mainly vaccine) and passive immunity (mainly monoclonal antibody). In terms of active immunity, ACI-35 vaccine is able to induce rapid immune response to p-tau in wild-type and transgenic p301L mice, improve tau pathology, and shows safety without any adverse inflammatory reactions<sup>[57]</sup>. Another anti-tau vaccine, AADvac1, is currently in phase 2 clinical trials for patients with mild to moderate AD<sup>[56]</sup>. Concerning passive immunity, two kinds of human anti-tau monoclonal antibodies ABBV-8E12 and RO7105705 are used in the treatment of early AD, prodromal stage and mild AD, respectively, which were under phase 2 clinical evaluation. In addition, three kinds of anti-tau monoclonal antibodies IIB076, JNJ-63733657 and LY3303560 are in phase 1 clinical trial<sup>[58]</sup>.

## 3 DRUG THERAPY FOR OTHER PATHOLOGICAL MECHANISMS OF AD

Although A $\beta$  formation and tau protein hyperphosphorylation are the two characteristic lesions of AD, the occurrence and development of AD cannot be fully explained by these two hallmarks of the disease. Neuroinflammatory reaction, neurotransmitter dysfunction, oxidative damage, mitochondrial dysfunction, neurodegenerative changes and neuron loss are all associated with the development and progression of AD and the occurrence of related symptoms. Therefore, in addition to the drugs that target A $\beta$  and tau protein, researchers have investigated other therapeutic strategies including: (1) anti-inflammation; (2) improvement of neurotransmitter imbalance; (3)

anti-oxidation and improvement of mitochondrial function; (4) protection of neurons; (5) promotion of neuronal regeneration (fig. 3).

Neuroinflammatory reaction, neurotransmitter dysfunction, oxidative damage, mitochondrial dysfunction, neurodegenerative changes and neuron loss are all proved to be involved in the pathology of AD. Thus, anti-inflammation, improving neurotransmitter imbalance, promoting neuron regeneration, protecting neurons, anti-oxidation and improving mitochondrial function may help improve AD.

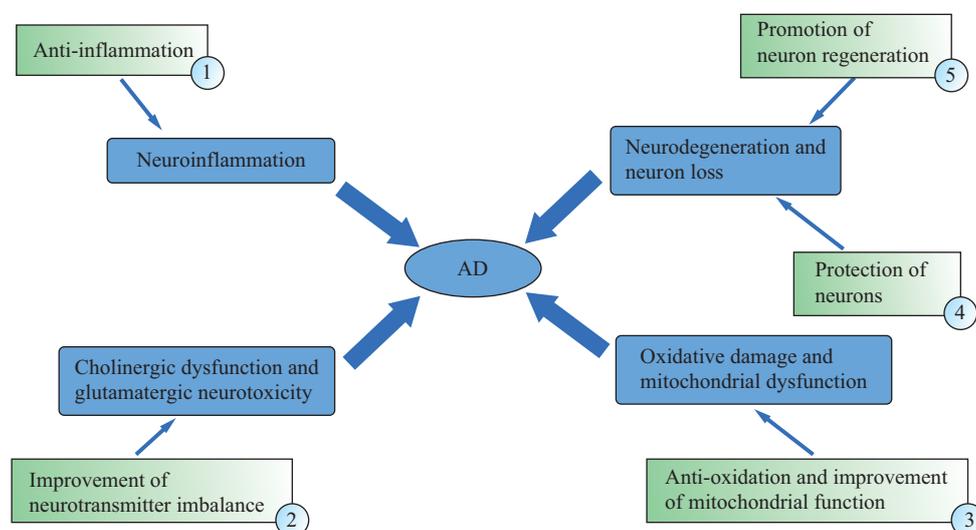
### 3.1 Anti-inflammation

Neuroinflammation plays an important role in the pathogenesis and progression of AD. Inflammatory factors are significantly increased in the brain of AD patients, and inflammation can cause neurodegenerative changes of AD<sup>[59]</sup>. Neuroinflammation in AD is different from the traditional definition of neuroinflammatory diseases (such as multiple sclerosis and encephalitis). It is mainly driven by microglia in the brain, rather than by B cells and T cells from the peripheral circulation<sup>[60]</sup>. Interestingly, studies have shown that acute and chronic systemic inflammation can lead to the increase of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which is related to the decline of cognitive function in AD<sup>[61]</sup>. Therefore, anti-inflammatory drugs could possibly improve the condition of AD. In line with this, the anti-inflammatory drug cromolyn alone or in combination with ibuprofen has been found to reduce the levels of A $\beta$  1-40 and A $\beta$  1-42 in the brain of transgenic AD mice, and induce the activation of neuroprotective microglia which is conducive to phagocytic clearance of A $\beta$ <sup>[62]</sup>. COR388 is a new molecule that targets the toxic proteases gingipains that are produced by *Porphyromonas gingivalis*. This *P. gingivalis* is found in more than 90% of post-mortem

AD patients' brains and revealed to induce Alzheimer's pathology in infected animals<sup>[63]</sup>. COR388 was found to significantly reduce the biomarkers of AD patients in clinical trials, and has a tendency to improve cognition. COR388 has now entered phase 2/3 clinical trial<sup>[64]</sup>. Another product, sodium oligomannate, a new drug independently developed in China, has shown safety and efficacy for mild to moderate AD in phase 2 clinical trials<sup>[65]</sup>. Studies have shown that the gut microbiota dysbiosis leads to the accumulation of peripheral phenylalanine and isoleucine and activates Th1 cells. Th1 cells infiltrating the brain promote microglia activation and AD neuroinflammation. Interestingly, sodium oligomannate was found to inhibit intestinal flora imbalance and neuroinflammation, thus improving cognitive impairment<sup>[65]</sup>. Several other anti-inflammatory drugs, such as Masitinib, GRF6019, AL002 and AL003, are also in clinical trials<sup>[58]</sup>.

### 3.2 Improvement of Neurotransmitter Imbalance

Cholinergic neurons are widely distributed in the human brain. The high-density cholinergic neurons in thalamus, striatum, limbic system and neocortex suggest their roles in learning, memory, attention and other higher brain functions. "Cholinergic hypothesis" points out that the degeneration of basal forebrain neurons in AD patients leads to dysfunction and death of cholinergic neurons in the forebrain, and then extensive presynaptic denervation occurs, which leads to the decline of cognitive function in AD patients<sup>[66]</sup>. Excitatory glutamatergic neurotransmission through NMDA receptors is essential for synaptic plasticity. Excessive NMDA receptor excitation can cause neurotoxicity and promote cell death<sup>[67]</sup>. In AD patients, the balance between synaptic and extra-synaptic glutamatergic transmission shifts to extra-synaptic sites, resulting in glutamate excitotoxicity<sup>[68]</sup>.



**Fig. 3** Other pathological mechanisms of AD and corresponding drug treatment strategies

(1): anti-inflammation; (2): improvement of neurotransmitter imbalance; (3): anti-oxidation and improvement of mitochondrial function; (4): protection of neurons; (5): promotion of neuronal regeneration

In addition, the adrenergic pathway in locus coeruleus and the serotonergic pathway are defective in AD patients, and somatostatin intermediate neurons and dopaminergic neurons in the cortex may also be affected<sup>[69]</sup>. These together suggest that the improvement of neurotransmitter imbalance could be helpful to alleviate AD.

Based on the “cholinergic hypothesis”, many researchers have paid attention to cholinesterase inhibitors (AChEI). Cholinesterase inhibitors prevent cholinesterase in synaptic space from hydrolyzing acetylcholine, thus enhancing cholinergic activity. It has been proved that cholinesterase inhibitors can effectively delay the decline of cognitive function in AD patients<sup>[66]</sup>. At present, there are only 6 kinds of drugs approved by FDA for AD treatment, of which 4 are AChEIs, namely tacrine, donepezil, galantamine and rivastigmine. For glutamate excitotoxicity, memantine, another FDA approved drug, is an NMDA receptor blocker which acts by specifically binding to NMDA receptor gated calcium channels and blocking NMDA mediated calcium influx, thus improving neuropathy caused by high levels of glutamate in AD patients<sup>[70]</sup>. In February 2020, Suvorexant (Belsomra), an orexin receptor antagonist, was approved by FDA to be the first medication for treating sleep disorders in AD (<https://www.alzforum.org/therapeutics/suvorexant>).

### 3.3 Antioxidation and Improvement of Mitochondrial Function

The structure and function of mitochondria of neurons in AD patients are damaged, and this is one of the early characteristics of AD. At the same time, as a result of mitochondrial dysfunction, the large molecules in neurons suffer from total oxidative damage, supporting the important role of oxidative stress in AD<sup>[71]</sup>. Because mitochondria are also easily affected by oxidative stress, mitochondrial dysfunction and oxidative stress interact to form a vicious cycle, producing a large number of reactive oxygen species (ROS), which may be the key mechanism of the pathogenesis and/or progression of AD.

Ginkgo biloba contains antioxidant components and helps to improve mitochondrial function. According to the data of the existing literature, the application of ginkgo biloba for 3 to 6 months can slightly improve the cognitive function of AD<sup>[72]</sup>. However, a clinical study showed that ginkgo biloba extract could not reduce the risk of AD in patients<sup>[73]</sup>. Deferiprone, an iron chelating agent, has the effect of reducing ROS and anti-A $\beta$  at the same time. Rasagline, a monoamine oxidase inhibitor, can enhance mitochondrial function and inactivate ROS, and also act on A $\beta$ . Both Deferiprone and Rasagline are currently in phase 2 clinical trial<sup>[25]</sup>. Feru-guard is a new compound which is a combination of ferulic acid (FA) and Angelica archangelica (AA) extract. When used for the treatment of behavioral and

psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies, Feru-guard was shown to significantly decrease overall Neuropsychiatric Inventory scores in 19 of 20 patients, suggesting that it has effects on behavioral and psychological symptoms of dementia<sup>[74]</sup>. Interestingly, in a 48-week multicenter randomized double-blind placebo-controlled prospective trial for MCI, the results showed a significant improvement in the Mini-Mental State Examination (MMSE) scores at 24 weeks, and at both 24 and 48 weeks for the Japanese evaluation scale<sup>[75]</sup>, indicating that Feru-guard could be beneficial for MCI. However, another study found that this compound does not reduce A $\beta$  deposition, nor does it suppress the aggravation of brain atrophy or decline in cognitive function<sup>[76]</sup>.

### 3.4 Protection of Neurons

Since AD is a neurodegenerative disease, protecting the neurons from degeneration could help fight AD. Neuron protection drugs include Cilostazol, a phosphodiesterase-3 (PDE-3) inhibitor, which can reduce A $\beta$  deposition and tau protein phosphorylation and improve cerebral blood circulation. At present, Cilostazol has been used as a neuroprotective agent in phase II clinical trials<sup>[25]</sup>. DHA, an omega-3 fatty acid rich in brain tissue, is effective in reducing A $\beta$  production and improving synaptic function. It is also used as a neuroprotective agent in phase 2 clinical trials<sup>[25]</sup>. In addition, many drugs such as AGB101, Troiluzole, Icosapent ethyl, AMX0035, LM11A-31-BHS and others are undergoing clinical trials as neuroprotective agents<sup>[25]</sup>.

### 3.5 Promotion of Neuron Regeneration

One of the characteristics of AD is the loss of neurons in the brain, and the number of neurons lost is directly related to the symptoms of AD. This suggests that promoting the neuronal growth or regeneration is also a feasible treatment of AD. Ndx-1017 is a hepatocyte growth factor, which may have the function of promoting neuron growth, and is currently in phase 1 clinical trial<sup>[25]</sup>. Stem cell therapy is also a common nerve growth promoting therapy. Astrostem, a kind of mesenchymal stem cells derived from adipose tissue and renewable neurons, is currently in phase 2 clinical trial<sup>[25]</sup>. Human umbilical cord blood mesenchymal stem cells (HUCB MSCs), may also regenerate neurons, reduce SP and reduce systemic inflammation of microglia. This led to the investigation on hMSCs, namely human mesenchymal stem cells, and both are now in phase 1 clinical trial<sup>[25]</sup>.

## 4 SUMMARY AND PROSPECT

Although a large amount of money and energy has been invested in the research and development of therapeutic drugs for AD, it is unfortunate to find out

that many of the DMT drugs fail in clinical trials due to safety and/or effectiveness problems. At present, the available drugs for clinicians are very limited, and all of them are symptomatic drugs, and thus could not stop the progression of the disease. This reminds us that we might need to change our thinking in order to better solve the current predicament. One feasible idea is drug combination therapy since AD is a multifactorial condition with complex etiopathogenesis. Compared with single therapy, combination therapy has many advantages, such as: (1) multiple drugs are more likely to reverse the pathological changes of AD; (2) multi-drug combination therapy is more effective than single drug treatment, and it is more likely to improve AD symptoms; (3) multi-drug combination therapy reduces the dosage of each drug, which can reduce the risk of adverse reactions. The mechanism of action may produce synergistic effect, which may improve the curative effect. At present, the combination therapy of AChEIs and memantine has been proved to have clinical efficacy<sup>[77]</sup>.

Many DMT drugs currently under study have shown improvement effect on early AD (prodromal stage, mild AD), but difficult to play a role in late stage (moderate and severe) AD. Therefore, prompt usage of DMT drugs in the early stage of AD pathological changes may be a better treatment strategy to tackle AD. However, higher requirements are put forward for the identification and diagnosis of early AD. At present, the early diagnosis of AD has not been fully established. For this, there is a need to explore biomarkers with high sensitivity and/or specificity, and improve the neuroimaging diagnosis technology of AD. In addition, the early detection of AD in the elderly (especially those over 60 years old) will be more conducive to the early diagnosis and prevention of AD.

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#### Conflict of Interest Statement

The authors declare that they have no competing interests.

#### REFERENCES

- 1 Wenk GL. Neuropathologic changes in Alzheimer's disease. *J Clin Psychiatry*, 2003,64(Suppl 9):7-10
- 2 Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol*, 2018,25(1):59-70
- 3 Howard R, McShane R, Lindesay J, *et al.* Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*, 2012,366(10):893-903
- 4 Hyde C, Peters J, Bond M, *et al.* Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model. *Age Ageing*, 2013,42(1):14-20
- 5 Cummings J, Lee G, Ritter A, *et al.* Alzheimer's disease drug development pipeline: 2020. *Alzheimers Dement (N Y)*, 2020,6(1):e12050
- 6 Portelius E, Dean RA, Gustavsson MK, *et al.* A novel A $\beta$  isoform pattern in CSF reflects  $\gamma$ -secretase inhibition in Alzheimer disease. *Alzheimers Res Ther*, 2010,2(2):7
- 7 Younkin SG. The role of A $\beta$ 42 in Alzheimer's disease. *J Physiol Paris*, 1998,92(3-4):289-292
- 8 Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*, 1992,256(5054):184-186
- 9 Yan R, Vassar R. Targeting the  $\beta$  secretase BACE1 for Alzheimer's disease therapy. *Lancet Neurol*, 2014,13(3):319-329
- 10 Huang LK, Chao SP, Hu CJ. Clinical trials of new drugs for Alzheimer disease. *J Biomed Sci*, 2020,27(1), DOI:10.1186/s12929-019-0609-7
- 11 Neumann U, Ufer M, Jacobson LH *et al.* The BACE-1 inhibitor CNP 520 for prevention trials in Alzheimer's disease. *EMBO Mol Med*, 2018,10(11):e9316
- 12 Shi X-P, Tugusheva K, Bruce JE, *et al.*  $\beta$ -Secretase cleavage at amino acid residue 34 in the amyloid  $\beta$  peptide is dependent upon  $\gamma$ -secretase activity. *J Biol Chem*, 2003,278(23):21286-21294
- 13 Sun X, He G, Song W. BACE2, as a novel APP  $\theta$ -secretase, is not responsible for the pathogenesis of Alzheimer's disease in Down syndrome. *FASEB J*, 2006,20(9):1369-1376
- 14 Fluhner R, Capell A, Westmeyer G, *et al.* A non-amyloidogenic function of BACE-2 in the secretory pathway. *J Neurochem*, 2002,81(5):1011-1020
- 15 Abdul-Hay SO, Sahara T, McBride M, *et al.* Identification of BACE2 as an avid  $\beta$ -amyloid-degrading protease. *Mol. Neurodegen*, 2012,7(1):1-12
- 16 Alic I, Goh PA, Murray A, *et al.* Patient-specific Alzheimer-like pathology in trisomy 21 cerebral organoids reveals BACE2 as a gene-dose-sensitive AD-suppressor in human brain. *Mol Psychiatry*, 2020, DOI:10.1038/s41380-020-0806-5
- 17 Kumar D, Ganeshpurkar A, Kumar D, *et al.* Secretase inhibitors for the treatment of Alzheimer's disease: Long road ahead. *Eur J Med Chem*, 2018,148:436-452
- 18 Henley DB, May PC, Dean RA, *et al.* Development of semagacestat (LY450139), a functional  $\gamma$ -secretase inhibitor, for the treatment of Alzheimer's disease. *Expert Opin Pharmacother*, 2009,10(10):1657-1664
- 19 Doody RS, Raman R, Farlow M, *et al.* A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*, 2013,369(4):341-350
- 20 Coric V, Salloway S, van Dyck CH, *et al.* Targeting

- prodromal Alzheimer disease with avagacestat: a randomized clinical trial. *JAMA Neurol*, 2015,72(11):1324-1333
- 21 Postina R. A closer look at  $\alpha$ -secretase. *Curr Alzheimer Res*, 2008,5(2):179-186
- 22 Marcade M, Bourdin J, Loiseau N, *et al.* Etazolate, a neuroprotective drug linking GABAA receptor pharmacology to amyloid precursor protein processing. *J Neurochem*, 2008,106(1):392-404
- 23 Lahiri DK, Chen D, Maloney B, *et al.* The experimental Alzheimer's disease drug posiphen [(+)-phenserine] lowers amyloid- $\beta$  peptide levels in cell culture and mice. *J Pharmacol Exp Ther*, 2007,320(1):386-396
- 24 Teich AF, Sharma E, Barnwell E, *et al.* Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse. *Alzheimers Dement (N Y)*, 2018,4(1):37-45
- 25 Cummings J, Lee G, Ritter A, *et al.* Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement (N Y)*, 2019,5:272-293
- 26 Wang J, Gu BJ, Masters CL, *et al.* A systemic view of Alzheimer disease—insights from amyloid- $\beta$  metabolism beyond the brain. *Nat Rev Neurol*, 2017,13(10):612
- 27 Mawuenyega KG, Sigurdson W, Ovod V, *et al.* Decreased clearance of CNS  $\beta$ -amyloid in Alzheimer's disease. *Science*, 2010,330(6012):1774-1774
- 28 Sevigny J, Chiao P, Bussière T, *et al.* The antibody aducanumab reduces A $\beta$  plaques in Alzheimer's disease. *Nature*, 2016,537(7618):50-56
- 29 Selkoe DJ. Alzheimer disease and aducanumab: adjusting our approach. *Nat Rev Neurol*, 2019,15(7):365-366
- 30 Hung SY, Fu WM. Drug candidates in clinical trials for Alzheimer's disease. *J Biomed Sci*, 2017,24(1):47
- 31 Vandenberghe R, Rinne JO, Boada M, *et al.* Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. *Alzheimer's Res Ther*, 2016,8(1):18
- 32 Panza F, Solfrizzi V, Imbimbo BP, *et al.* Amyloid-directed monoclonal antibodies for the treatment of Alzheimer's disease: the point of no return? *Expert Opin Biol Ther*, 2014,14(10):1465-1476
- 33 Ostrowitzki S, Lasser RA, Dorflinger E, *et al.* A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimer's Res Ther*, 2017,9(1):95
- 34 Tariot PN, Lopera F, Langbaum JB, *et al.* The Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Trial: A study of crenezumab versus placebo in preclinical PSEN1 E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease, including a placebo-treated noncarrier cohort. *Alzheimers Dement (N Y)*, 2018,4:150-160
- 35 Boada M, López O, Núñez L, *et al.* Plasma exchange for Alzheimer's disease Management by Albumin Replacement (AMBAR) trial: Study design and progress. *Alzheimers Dement (N Y)*, 2019,5:61-69
- 36 Wiessner C, Wiederhold KH, Tissot AC, *et al.* The second-generation active A $\beta$  immunotherapy CAD106 reduces amyloid accumulation in APP transgenic mice while minimizing potential side effects. *J Neurosci*, 2011,31(25):9323-9331
- 37 Wang CY, Wang PN, Chiu MJ, *et al.* UB-311, a novel UBITH $\beta$  amyloid  $\beta$  peptide vaccine for mild Alzheimer's disease. *Alzheimers Dement (N Y)*, 2017,3(2):262-272
- 38 Dodel R, Du Y, Depboylu C, *et al.* Intravenous immunoglobulins containing antibodies against  $\beta$ -amyloid for the treatment of Alzheimer's disease. *J Neurol Neurosurg Psychiatry*, 2004,75(10):1472-1474
- 39 Dodel R, Neff F, Noelker C, *et al.* Intravenous immunoglobulins as a treatment for Alzheimer's disease. *Drugs*, 2010,70(5):513-528
- 40 Dodel R, Rominger A, Blennow K, *et al.* P4-411: A randomized, double-blind, placebo-controlled dose-finding trial of intravenous immunoglobulin (IVIG; Octagam $\text{\textcircled{R}}$  10%, Octapharma AG) in patients with mild to moderate Alzheimer's disease (GAM10-04). *Alzheimers Dement*, 2011,7:e55-e56
- 41 Kadavath H, Hofele RV, Biernat J, *et al.* Tau stabilizes microtubules by binding at the interface between tubulin heterodimers. *Proc Natl Acad Sci*, 2015,112(24):7501-7506
- 42 Wang JZ, Tian Q. Mechanisms of Tau hyperphosphorylation and its role in neuronal degeneration in Alzheimer's disease (In Chinese). *Adv Biochem Biophysics*, 2012,39(8):771-777
- 43 Alonso AdC, Grundke-Iqbal I, Iqbal K. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. *Nat Med*, 1996,2(7):783-787
- 44 Feinstein SC, Wilson L. Inability of tau to properly regulate neuronal microtubule dynamics: a loss-of-function mechanism by which tau might mediate neuronal cell death. *Biochim Biophys Acta Mol Basis Dis*, 2005,1739(2-3):268-279
- 45 Wang JZ, Xia YY, Grundke-Iqbal I, *et al.* Abnormal hyperphosphorylation of tau: sites, regulation, and molecular mechanism of neurofibrillary degeneration. *J Alzheimers Dis*, 2013,33(Suppl 1):S123-S139
- 46 Sereno L, Coma M, Rodriguez M, *et al.* A novel GSK-3 $\beta$  inhibitor reduces Alzheimer's pathology and rescues neuronal loss *in vivo*. *Neurobiol Dis*, 2009,35(3):359-367
- 47 Zhang X, Heng X, Li T, *et al.* Long-term treatment with lithium alleviates memory deficits and reduces amyloid- $\beta$  production in an aged Alzheimer's disease transgenic mouse model. *J Alzheimers Dis*, 2011,24(4):739-749
- 48 Morris G, Berk M. The putative use of lithium in Alzheimer's disease. *Curr Alzheimer Res*, 2016,13(8):853-861
- 49 van Eersel J, Ke YD, Liu X, *et al.* Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. *Proc Natl Acad Sci USA*, 2010,107(31):13888-13893
- 50 Malpas CB, Vivash L, Genc S, *et al.* A phase IIa randomized control trial of VEL015 (Sodium Selenate) in mild-moderate Alzheimer's disease. *J Alzheimers Dis*, 2016,54(1):223-232
- 51 Chohan MO, Khatoun S, Iqbal IG, *et al.* Involvement of I2PP2A in the abnormal hyperphosphorylation of tau and its reversal by memantine. *FEBS Lett*, 2006,580(16):3973-3979
- 52 Iqbal K, Zaidi T, Wen G, *et al.* Defective brain

- microtubule assembly in Alzheimer's disease. *Lancet*, 1986,328(8504):421-426
- 53 Defensor E, Farmer G, Gan L, *et al.* Effects of TPI 287, a novel taxoid, on a transgenic mouse model of Alzheimer's disease. In: *Neuroscience Meeting Planner*, Washington, DC: Society for Neuroscience, Online, 2014
- 54 Tsai RM, Miller Z, Koestler M, *et al.* Reactions to multiple ascending doses of the microtubule stabilizer TPI-287 in patients with Alzheimer disease, progressive supranuclear palsy, and corticobasal syndrome: a randomized clinical trial. *JAMA Neurol*, 2020,77(2):215-224
- 55 Paban V, Manrique C, Filali M, *et al.* Therapeutic and preventive effects of methylene blue on Alzheimer's disease pathology in a transgenic mouse model. *Neuropharmacology*, 2014,76:68-79
- 56 Pedersen JT, Sigurdsson EM. Tau immunotherapy for Alzheimer's disease. *Trends Mol Med*, 2015,21(6):394-402
- 57 Theunis C, Crespo-Biel N, Gafner V, *et al.* Efficacy and safety of a liposome-based vaccine against protein Tau, assessed in tau. P301L mice that model tauopathy. *PLoS One*, 2013,8(8):e72301
- 58 Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. *J Cent Nerv Syst Dis*, 2020,12:1179573520907397
- 59 Rogers J, Webster S, Lue LF, *et al.* Inflammation and Alzheimer's disease pathogenesis. *Neurobiol Aging*, 1996,17(5):681-686
- 60 Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. *Nat Rev Neurosci*, 2015,16(6):358-372
- 61 Holmes C, Cunningham C, Zotova E, *et al.* Systemic inflammation and disease progression in Alzheimer disease. *Neurology*, 2009,73(10):768-774
- 62 Zhang C, Griciuc A, Hudry E, *et al.* Cromolyn reduces levels of the Alzheimer's disease-associated amyloid  $\beta$ -protein by promoting microglial phagocytosis. *Sci Rep*, 2018,8(1):1-9
- 63 Dominy SS, Lynch C, Ermini F, *et al.* Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci Adv*, 2019,5(1):eaau3333
- 64 Detke M, Lynch C, Holsinger L, *et al.* COR388 for the Treatment of Alzheimer's Disease (4098). In: *AAN Enterprises*, 2020
- 65 Wang X, Sun G, Feng T, *et al.* Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res*, 2019,29(10):787-803
- 66 Hampel H, Mesulam MM, Cuello AC, *et al.* The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain*, 2018,141(7):1917-1933
- 67 Wang R, Reddy PH. Role of glutamate and NMDA receptors in Alzheimer's disease. *J Alzheimers Dis*, 2017,57(4):1041-1048
- 68 Zádori D, Veres G, Szalárdy L, *et al.* Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenes. *J Alzheimers Dis*, 2018,62(2):523-547
- 69 Hardy J, Adolfsson R, Alafuzoff I, *et al.* Transmitter deficits in Alzheimer's disease. *Neurochem Int*, 1985, 7(4):545-563
- 70 Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. *PloS One*, 2015,10(4):e0123289
- 71 Wang X, Wang W, Li L, *et al.* Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim Biophys Acta Mol Basis Dis*, 2014,1842(8): 1240-1247
- 72 Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol*, 1998,55(11):1409-1415
- 73 Vellas B, Coley N, Ousset PJ, *et al.* Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. *Lancet Neurol*, 2012,11(10):851-859
- 74 Kimura T, Hayashida H, Murata M, *et al.* Effect of ferulic acid and Angelica archangelica extract on behavioral and psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies. *Geriatr Gerontol Int*, 2011,11(3):309-314
- 75 Kudoh C, Hori T, Yasaki S, *et al.* Effects of Ferulic Acid and Angelica archangelica Extract (Feru-guard®) on Mild Cognitive Impairment: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Prospective Trial. *J Alzheimers Dis Rep*, 2020(Preprint):1-6
- 76 Matsuyama K, Yamamoto Y, Sora I. Effect of Feru-guard 100M on amyloid-beta deposition in individuals with mild cognitive impairment. *Psychogeriatrics*, 2020,20(5):726-736
- 77 Kabir M, Uddin M, Mamun AA, *et al.* Combination drug therapy for the management of Alzheimer's disease. *Int J Mol Med Sci*, 2020,21(9):3272

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