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# Based on molecular structures: Amyloid- $\beta$ generation, clearance, toxicity and therapeutic strategies

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Amyloid- $\beta$  (A $\beta$ ) has long been considered as one of the most important pathogenic factors in Alzheimer's disease (AD), but the specific pathogenic mechanism of A $\beta$  is still not completely understood. In recent years, the development of structural biology technology has led to new understandings about A $\beta$  molecular structures, A $\beta$  generation and clearance from the brain and peripheral tissues, and its pathological toxicity. The purpose of the review is to discuss A $\beta$  metabolism and toxicity, and the therapeutic strategy of AD based on the latest progress in molecular structures of A $\beta$ . The A $\beta$  structure at the atomic level has been analyzed, which provides a new and refined perspective to comprehend the role of A $\beta$  in AD and to formulate therapeutic strategies of AD.

## KEYWORDS

Alzheimer's disease, amyloid- $\beta$ , molecular structure, toxicity, therapeutic strategies

## Background

Alzheimer's disease (AD), which accounts for about 70% dementia, is the most common form of dementia. By 2050, global AD patients will triple in the number of 2010, with an incidence rate of 106.2/1 millions (Polanco et al., 2018). The pathological features of AD are amyloid plaques formed by amyloid- $\beta$  (A $\beta$ ) deposition

Abbreviations: AD, Alzheimer's disease; A $\beta$ , amyloid- $\beta$ ; sNMR, solid-state nuclear magnetic resonance; Cryo-EM, cryo-electron microscopy; APP, amyloid precursor protein; C<sub>83</sub>,  $\alpha$  secretase C-terminal fragment; sAPP $\beta$ , soluble APP $\beta$ ; C<sub>99</sub>,  $\beta$  secretase C-terminal fragment; AICD, APP intracellular domain; BBB, blood-brain barrier; HMGB1, high mobility group protein-1; LTP, long-term potentiation; LRP1, low density lipoprotein receptor-related protein-1; RAGE, receptor for advanced glycation endproducts; ISF, interstitial fluid; CKD, chronic kidney disease; MCI, mild cognitive impairment; OC, osteoclast; T2DM, type 2 diabetes mellitus; IAPP, islet amyloid polypeptide; BACE1,  $\beta$ -site amyloid precursor protein cleaving enzyme 1; GSI,  $\gamma$ -secretase inhibitor; NEP, enkephalinase; UCH-L1, ubiquitin C-terminal hydrolase L1; p75NTR, neurotrophin receptor p75; p75ECD, neurotrophin receptor p75 extracellular domain.

and neurofibrillary tangles formed by tau deposition (Hardy and Higgins, 1992; Sevigny et al., 2017). Current challenges in AD management include the lack of biomarkers that can be used for early diagnosis, and effective prevention and therapeutic strategies. The pathogenesis of AD involves abnormal metabolism and deposition of A $\beta$ , hyperphosphorylation of tau, oxidative stress response, inflammatory changes of glia and microglia cells and other pathological events. Among them, the hypothesis of A $\beta$  cascade is considered to be the most acceptable theory in the pathogenic mechanism of AD (Hardy and Higgins, 1992), although a few scholars doubt it (Wang, 2014; Herrup, 2015). In the past, A $\beta$  was thought to be only associated with central nervous system (CNS) diseases such as AD or cerebral amyloid angiopathy (CAA), and scholars focused on its metabolic and toxic effects in the brain. However, more and more experimental results, epidemiological and clinical evidences show that the pathological role of A $\beta$  is far beyond the CNS, and A $\beta$  also has a toxicity in plasma, bone, and other peripheral organs (Li et al., 2014; Michno et al., 2021; Tian et al., 2021). In recent years, with the development of molecular biology techniques such as solid-state nuclear magnetic resonance (sNMR) and cryo-electron microscopy (Cryo-EM), the structure of A $\beta$  was elucidated at the molecular and even atomic level, deepening the understanding of A $\beta$  toxic mechanism. A detailed analysis of A $\beta$  molecular structures and its toxicity mechanisms could improve current diagnostic and therapeutic strategies for AD and make it possible to design anti-A $\beta$  drugs precisely. In the future, A $\beta$  research may focus on some forms or structures of A $\beta$  in the plasma or cerebrospinal fluid as a reliable indicator of the early diagnosis of AD; designing drugs or treatment strategies based on the molecular mechanism of A $\beta$  oligomerization or fiber formation process and toxic effects; exploring the role of A $\beta$  in the pathology of AD and treating AD beyond the CNS; exploring the toxic effects of A $\beta$  on peripheral organs, such as whether it affects osteogenesis and osteoclasts of bone, whether it damages endothelial cells and smooth muscle cells of vessel, and whether its peripheral toxicity mechanism is also through the destruction of mitochondrial function and structure? Our review will describe the production, structure, and toxic effects in the brain, peripheral tissues, and plasma based on the different molecular structures and forms of A $\beta$ , the relationship between A $\beta$  and non-AD diseases, and possible therapeutic strategies for A $\beta$ .

## Molecular structure of amyloid- $\beta$

Amyloid- $\beta$  is a peptide consisting of 38–43 amino acid residues, mainly A $\beta_{42}$  and A $\beta_{40}$ , which can induce

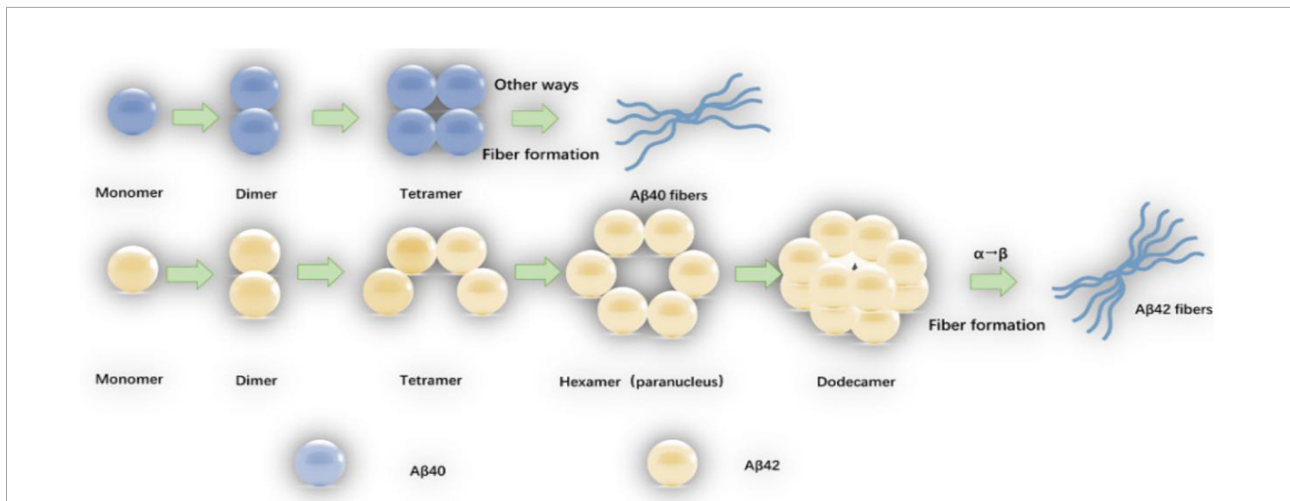
toxicity by aggregating in the brain and other organs. Understanding the molecular structure of A $\beta$  is of great significance for understanding the metabolic processes and pathological effects of various aggregation states of A $\beta$ . All A $\beta$  exists in three forms, including monomers, oligomers, and fibrils. Study indicated that A $\beta_{43}$ , an overlooked species, is potently amyloidogenic, neurotoxic and abundant *in vivo*. Also A $\beta_{43}$  may play a major role in AD, as plaques contain more A $\beta_{43}$  than A $\beta_{40}$  (Welander et al., 2009).

## Monomer and oligomer structure

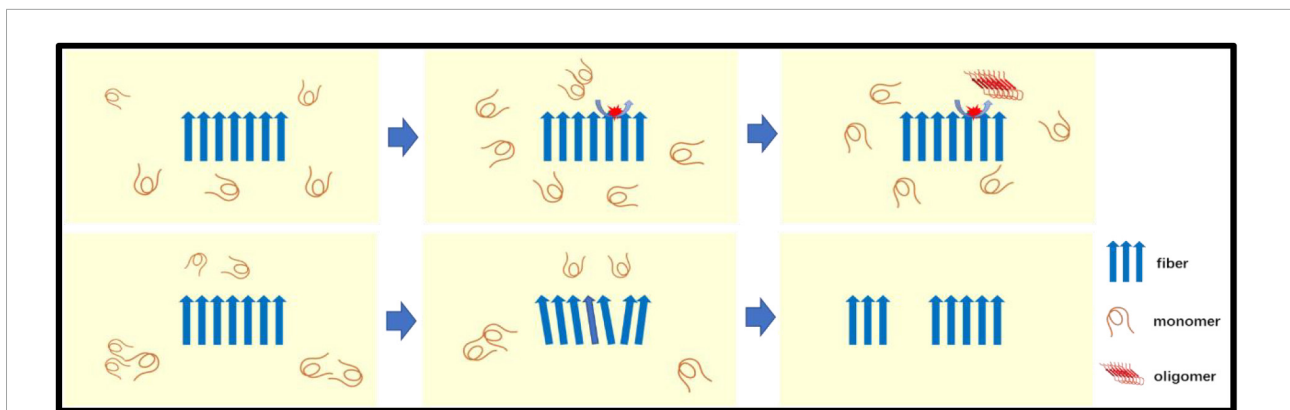
The natural A $\beta_{42}$  and A $\beta_{40}$  monomers are random coil structures or  $\alpha$ -helix. During the formation of A $\beta$  fibers, the monomer structure of A $\beta_{42}$  and A $\beta_{40}$  changes from natural structure to  $\beta$ -sheet (Rochet and Lansbury, 2000; Serpell et al., 2000; Sarroukh et al., 2011).

Amyloid- $\beta$  oligomers have a variety of structures which are formed spontaneously by folded or partially folded A $\beta$  monomers. The A $\beta$  oligomers under physiological conditions are at most 20-mer, and the tetramer is the determinant of the formation of hexamers and dodecamers (Nguyen and Derreumaux, 2014). A $\beta_{40}$  exists only in the form of dimers, trimers, and tetramers, and the A $\beta_{40}$  tetramer (ring structure) is tightly structured, resisting the addition of monomers or dimers, and does not form hexamers (sub-nuclei), but the A $\beta_{40}$  fibers can be slowly formed by other means (Bitan et al., 2003; Bernstein et al., 2009). A $\beta_{42}$  tetramer (bending structure) allows the addition of monomers or dimers to form pentamer and hexamer of a planar hexagonal structure, and two subnuclear hexamers are combined into a stacked sub-nuclear dimer [((A $\beta_{42}$ )<sub>6</sub>)<sub>2</sub>, dodecamer] (Chen and Glabe, 2006). The A $\beta$  monomer structure change that  $\alpha$ -helix converts to  $\beta$ -sheet (the rate limiting step in which the oligomer forms fibers) may occur on the A $\beta_{42}$  dodecamer level (Bernstein et al., 2009). The oligomerization and fiber formation of A $\beta_{42}$  and A $\beta_{40}$  are shown in Figure 1.

Secondary nucleation involves two ways for catalyzing nucleation on the surface of A $\beta$  fibers and fiber breakage (Figure 2). The aggregated A $\beta$  monomer structure is partially unfolded, misfolded or inherently disordered. Some molecules must first be aggregated into the nucleus, and A $\beta$  is then aggregated from the nucleus, so the formation of the nucleus determines the reaction rate. Experimental evidence indicates that such nuclei may be oligomers of different structural properties that differ from the final A $\beta$  fiber structure. After the formation of the nucleus, the addition of the monomer becomes faster. There may be intermediates such as fibrils present. Catalyzing nucleation on the surface of A $\beta$  fibers—the surface of A $\beta$  fibers can catalyze the production of new nuclei. Fiber breakage-A $\beta$



**FIGURE 1**  
 The oligomerization and fiber formation of Aβ<sub>42</sub> and Aβ<sub>40</sub>: The monomers of Aβ<sub>42</sub> and Aβ<sub>40</sub> first form a dimer, and a dimer further forms a tetramer. The tetrameric Aβ<sub>42</sub> structure (bending structure) is can be added with Aβ<sub>42</sub> monomer or dimer to form Aβ<sub>42</sub> hexamer (sub-nucleus). The two Aβ<sub>42</sub> hexamers form a dodecamer (one stack paranuclear dimer). The natural structure of the Aβ<sub>42</sub> monomer is converted to a β-sheet structure (the rate-limiting step in which the oligomer forms fibers) occurs at the 12-mer level. The tetrameric Aβ<sub>40</sub> is in a ring structure, resisting further addition of Aβ<sub>40</sub> monomer or dimer, fibers are also formed by other means.



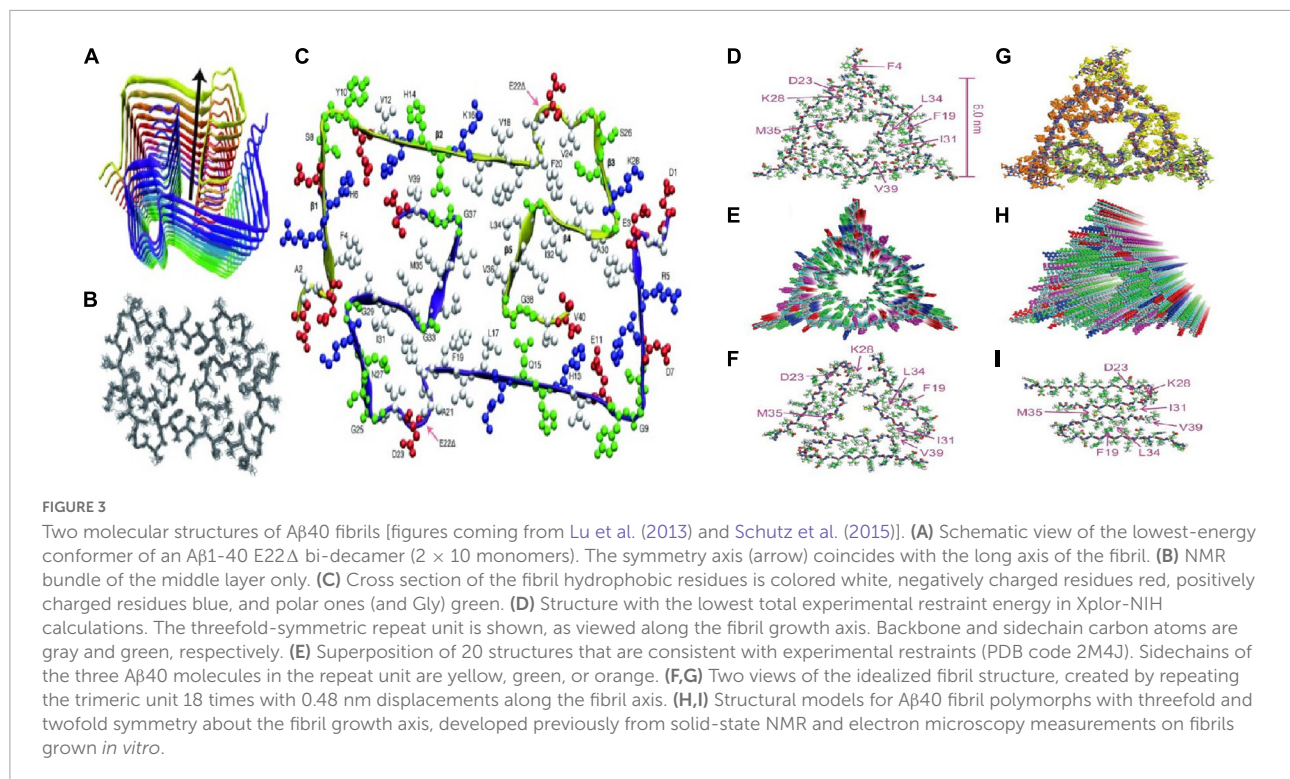
**FIGURE 2**  
 The secondary nucleation: Secondary nucleation includes two ways for catalyzing nucleation on the surface of Aβ fibers (top panel) and fiber breakage (bottom panel). Aβ monomer is catalyzed to form oligomers (new nuclei) on the surface of fibers. The Aβ fiber recruitment monomer is further extended by recruiting monomers and the ever-expanding fiber can be broken into two seeds (short segments) as a new aggregated nuclei.

fiber recruitment monomer is further extended and the ever-expanding fibers can be broken into two short segments as new aggregated nuclei.

### Fiber structure

Petkova et al. (2002) analyzed Aβ<sub>40</sub> fibers by sNMR and X-ray diffraction: (1) amino acid residues 12–24 and 30–40 adopt β-strand conformations and form parallel β-sheets by intermolecular hydrogen bonding; (2) the 25–29 residue contains a bended peptide backbone that brings two β-sheets to

the interaction via the sidechain-sidechain; (3) the single cross-β unit is a double-layer β-sheet structure having a hydrophobic core and surface; (4) the only charged side chains in its hydrophobic core are D23 and K28, which form a salt bridges between them; (5) fibers with minimum mass length and diameter are composed of two cross-β units, with hydrophobic surfaces juxtaposed. In addition, Bertini et al. (2011) found that the addition of new inter-monomers occurred at the protofilament interface during the elongation of Aβ<sub>40</sub> fiber. Lu et al. (2013) and Schutz et al. (2015) obtained Aβ<sub>40</sub> fiber structures in their respective sNMR studies (Figure 3), these fiber structures have some the commonalities. Residue 1–10



structure is disordered, residues 12–24 and 30–40 constitute two  $\beta$ -chains and form a  $\beta$ -sheet by intermolecular hydrogen bonding, and residues 25–29 constitute a curved portion of the peptide backbone and the two  $\beta$ -strands are in contact through the interaction between the side chains.

Schmidt et al. (2015) analyzed the characteristics of A $\beta$ <sub>42</sub> fiber structure with Cryo-EM: (1) peptide dimers packed face to face form the individual layers of the A $\beta$ <sub>42</sub> fibril; (2) these two peptides form a dimer with the same tilde-shaped conformation and interaction through the hydrophobic C-terminal  $\beta$ -strands package; (3) the C-terminus of the peptide is close to the fibril axis, creating a hydrophobic core on the fibril axis, surrounded by a structurally more flexible, charged peptide N-terminal segment. Colvin et al. (2016) and Walti et al. (2016) resolved the spatial structure of residues 15–42 in A $\beta$ <sub>42</sub> fibers by Snmr, respectively. It is believed that the fiber polymorph is mainly affected by the C-terminus and the two protofilament in the fiber are 2<sup>1</sup>-spiral symmetry. Gremer et al. (2017) analyzed the molecular structure of all residues of A $\beta$ <sub>42</sub> fiber by Cryo-EM, and proposed that six A $\beta$ <sub>42</sub> monomers constitute the smallest fiber unit, in which each two monomers constitute a dimer plane, and the existence of the inter-ion ionic bond in the A $\beta$ <sub>42</sub> fiber and the “LS” conformation of the monomer in the A $\beta$ <sub>42</sub> fiber were clearly confirmed (the N-terminus is L-form and the C-terminus is S-type) (Figure 4).

## The relationship between molecular structure and generation of amyloid- $\beta$

Amyloid- $\beta$  is a regulated cleavage product of amyloid precursor protein (APP), so APP metabolism has a direct effect on A $\beta$  generation. APP mainly has three isomers, which are APP<sub>695</sub>, APP<sub>751</sub>, and APP<sub>770</sub>. APP<sub>695</sub> is mainly expressed in neurons, while APP<sub>695</sub> and APP<sub>751</sub> is mainly expressed in glial cells and other peripheral cells, APP<sub>770</sub> is expressed in vascular endothelial cells. A $\beta$ <sub>42</sub> and A $\beta$ <sub>40</sub> are main components of senior plaques within the brain of AD and are regarded to as an initiating factor for the pathogenesis of AD (Del Turco et al., 2016). Closely related to the onset of AD, A $\beta$ <sub>42</sub> is present in the brain as a physiological factor, as well as A $\beta$ <sub>40</sub>. There are more A $\beta$ <sub>40</sub> in AD brain than A $\beta$ <sub>42</sub>, but A $\beta$ <sub>42</sub> is more toxic than A $\beta$ <sub>40</sub> (Haass and Selkoe, 2007).

Amyloid precursor protein is cleaved in different subcellular regions, eventually producing A $\beta$ <sub>42</sub> or A $\beta$ <sub>40</sub>. Pathways of amyloid precursor protein (APP) processing and amyloid- $\beta$  (A $\beta$ ) generation are shown in Figure 5. Zhang et al. (2011) summarized the basic steps. Firstly, after translation in the endoplasmic reticulum (ER) APP is further modified in the ER and Golgi. Secondly, APP is transported to the cell membrane by vesicles. Thirdly, APP is cut in two ways on the cell membrane. One way is non-amyloid protein pathway, APP is cleaved by  $\alpha$ -secretase on the membrane to generate soluble



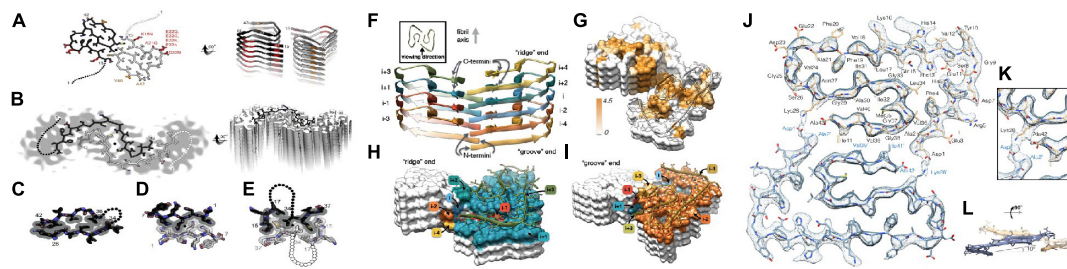


FIGURE 4

Two molecular models of A $\beta$ 42 fibrils architecture and atomic model of the fibril cross section [figures coming from Eisenberg and Sawaya (2016) and Gremer et al. (2017)]. (A) The near-atomic resolution model determined by solid-state NMR by Wälti et al. Two double-horseshoe-shaped molecules of amyloid- $\beta$ (1–42) are shown (black and gray) related by a twofold axis (marked by a circle), which runs down the center of the fibril. The N-terminal 14 residues are disordered; one possible conformation is shown here by dotted lines. Many of the known familial mutations are carried by residues located on the outer surface (red). The surface hydrophobic patch formed by residues V40 and A42 (orange) may explain the greater rate of secondary nucleation by the 1–42 species compared with 1–40. (B) The lower resolution (5–7 Å) model determined by Schmidt et al. by cryo-EM is another polymorph of amyloid- $\beta$ (1–42), also with two molecules per layer, related by a twofold axis, and also with a poorly ordered N terminus. The gray color represents a slice through the cryo-EM map. The two molecules appear to be related by a homo-steric zipper type of bonding. In both A and B, the models are viewed down the fibril axis on the left and nearly perpendicular to the fibril axis on the right. (C) A hetero-zipper in amyloid- $\beta$ (1–42) fibrils from Wälti et al. (D) A homo-zipper from GNNQNY. (E) A noncontiguous homo-zipper from Wälti et al. Dotted lines represent intervening residues. (F) Side view of the atomic model showing the staggered arrangement of the non-planar subunits. (G) Surface representation of a fragment of the atomic fibril model. The surface is colored according to hydrophobicity (Kyte-Doolittle scale) [gradient from brown (hydrophobic, 4.5) to white (neutral, 0.0)]. View of the “ridge” (H) and “groove” (I) fibril ends. (J) Two subunits, one from each protofilament, are shown (blue and brown) together with the masked EM density map. (K) Detailed view of the interactions between the N- and C-terminus and the sidechain of Lys28 (at contour level of 1  $\sigma$ ). (L) Side view of the same two opposing subunits showing the relative orientation of the non-planar subunits.

APP $_{\alpha}$  and  $\alpha$  secretase C-terminal fragment (C $_{83}$ ). Another way is amyloid pathway,  $\beta$ -secretase cleaves APP into soluble APP $_{\beta}$  (sAPP $_{\beta}$ ) and  $\beta$  secretase C-terminal fragment (C $_{99}$ ) in endosomes. Fourthly,  $\gamma$ -secretase complex cleaves C $_{99}$  into the APP intracellular domain (AICD) and A $\beta$ . In recent years, there has been a new understanding of the process of A $\beta$  generation. Firstly, it was previously thought that  $\beta$ -secretase cleaves APP on the cell membrane, but Das et al. (2013) found that APP and  $\beta$ -secretase were internalized into the cell to form endosomes, and then fuse in the endosomes, and then cut the APP into sAPP $_{\beta}$  and C $_{99}$  by  $\beta$ -secretase in 2013. Secondly, it was thought that the  $\gamma$ -secretase cleavage site was on the cell membrane in the past, but Area-Gomez et al. (2009, 2012) found that the  $\gamma$ -secretase cleavage might occur in mitochondrial membrane, multivesicular body and lysosome in 2012. Thirdly, it was previously thought that C $_{83}$  could not generate A $\beta$ , but Siegel et al. (2017) found that C $_{83}$  generated a small amount of A $\beta$  in 2017.

Lys28, and Val40-ALA42 (only A $\beta$ 42) are tightly bound by hydrophobic interactions, extending along the surface of A $\beta$  fibers, which may affect cell viability; secondly, formed A $\beta$  fiber breakage produces two short fragments for replication, resulting in more A $\beta$  fiber formation; Thirdly, A $\beta$  peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae (Hansson Petersen et al., 2008). A $\beta$  fibers bind to the mitochondrial membrane, interfering with the function of the oxidative respiratory chain type I complex. In addition, a considerable amount of A $\beta$  is produced at mitochondria ER contact sites including outer mitochondrial membrane and mitochondria-associated ER membranes. Enhanced A $\beta$  production at this site may disturb ER, mitochondrial and mitochondria-ER contact site function (Schreiner et al., 2015). Fourthly, A $\beta$  fiber surface catalyzes the formation of new A $\beta$  oligomers, generating greater toxic effects (Rhein et al., 2009; Cohen et al., 2013; Riek and Eisenberg, 2016).

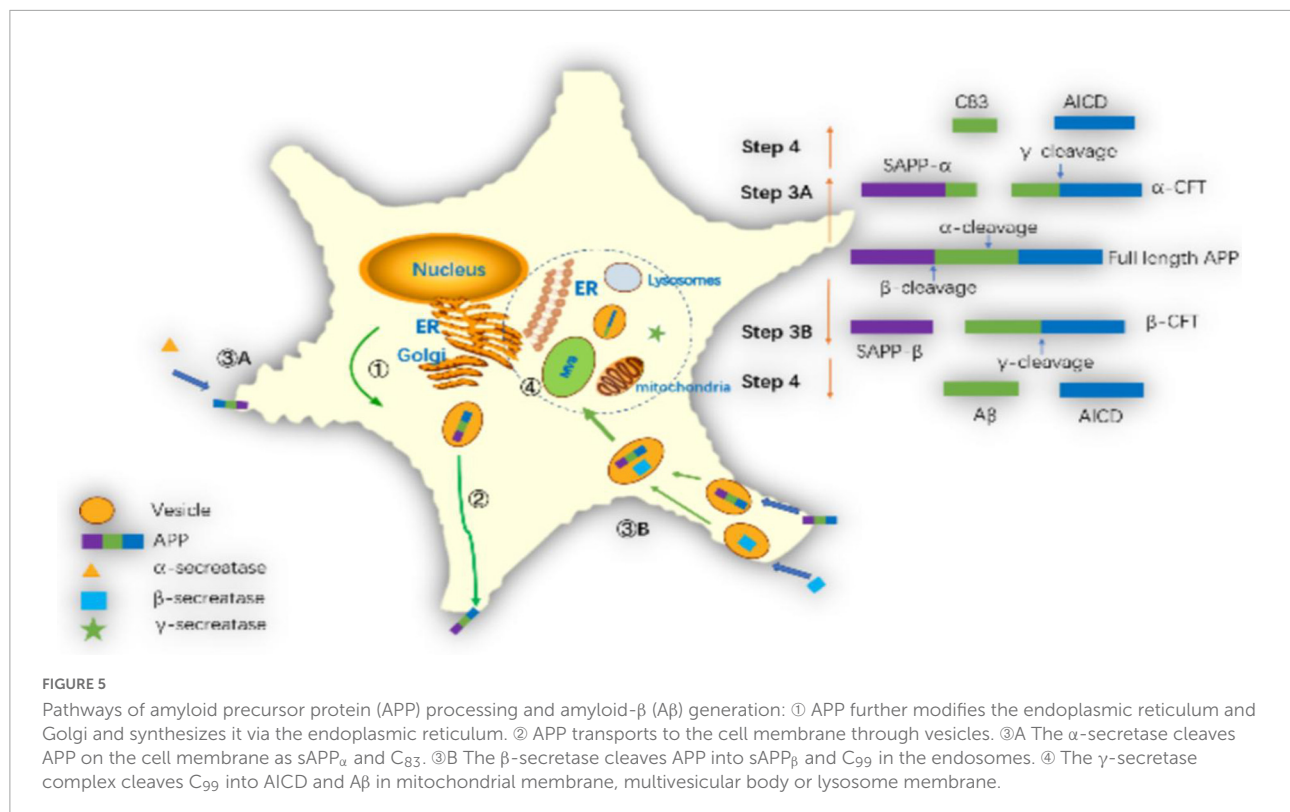
## The relationship between molecular structure and toxicity of amyloid- $\beta$

### Toxicity of amyloid- $\beta$ fiber

Amyloid- $\beta$  fiber mainly induces toxicity through four ways. Firstly, three hydrophobic groups consisting of Val18-ALA21,

### Toxicity of amyloid- $\beta$ oligomers

Amyloid- $\beta$  oligomers are short polymers in which a small amount of A $\beta$  monomers are linked by covalent bond repeats, and their toxic effects have been well confirmed (Figure 6) (Lambert et al., 1998; Hsia et al., 1999). Endogenous A $\beta$  oligomers are 1,000 times more toxic than synthetic soluble A $\beta$  monomers (Bateman et al., 2019). A $\beta$  dimer accumulates in lipid rafts (lipid regions of cell membranes), promotes A $\beta$  aggregation



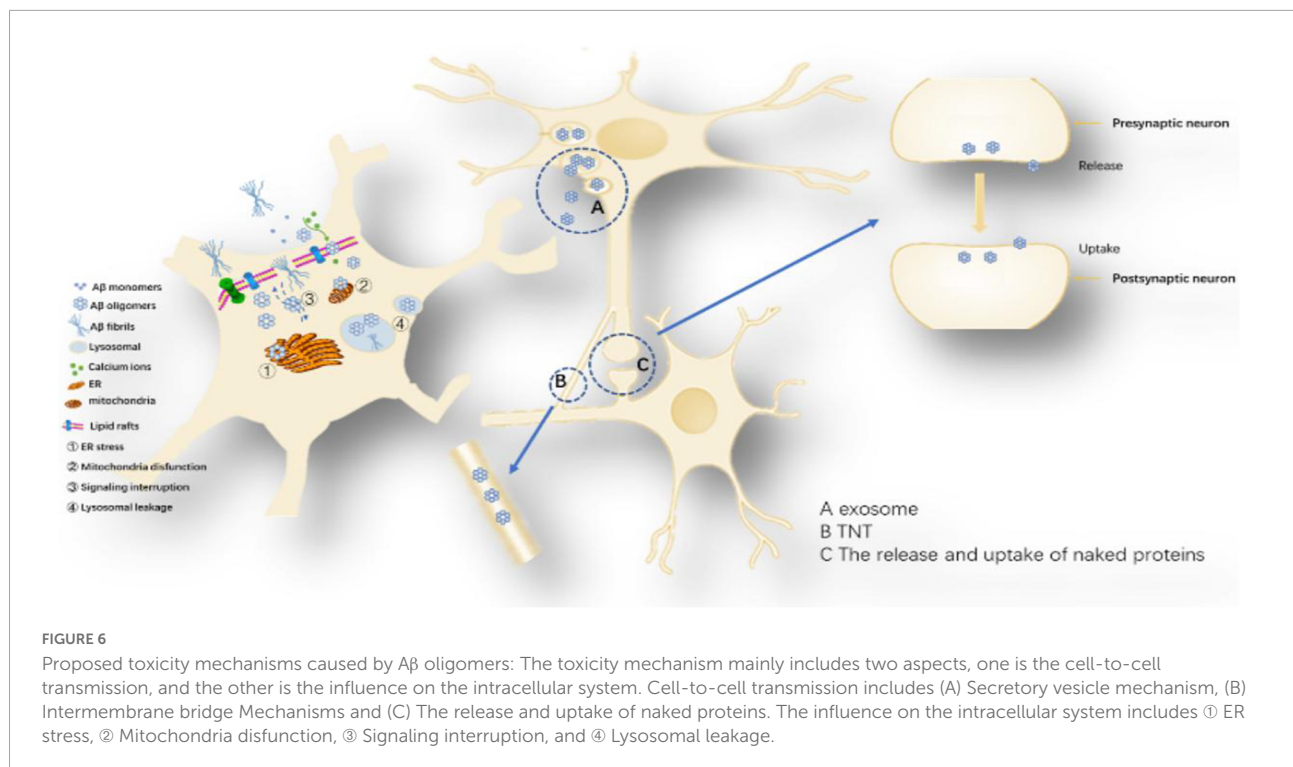
and plaque formation, and its accumulation time is consistent with the time of memory loss, impairing memory function (Kawarabayashi et al., 2004; Shankar et al., 2008; Hong et al., 2014).  $A\beta$  trimers have the strongest ability to attenuate long-term potentiation (LTP) and can trigger abnormal cell signaling to reduce electrical activity in hippocampal synapses (Townsend et al., 2006; Talantova et al., 2013). We know that the dimers, trimers, and tetramers of  $A\beta$  are shared by  $A\beta_{40}$  and  $A\beta_{42}$ , and the toxicity of pentameric and above structures is only  $A\beta_{42}$ . The hollow tube structure (C-terminal outward) of  $A\beta_{42}$  hexa- or 12-mer can form a cyclic structure on the membrane to destroy its integrity, which can damage the memory function of AD mice, leading to neuronal death and neurodegeneration (Lesne et al., 2006; Bernstein et al., 2009; Miller et al., 2010).

Amyloid- $\beta$  oligomerization internalization triggers intracellular systemic damage, increases ER stress levels, mediates calcium imbalance leading to decreased cell viability and activation of apoptotic caspase 3 (Resende et al., 2008; Umeda et al., 2011; Economou et al., 2016).  $A\beta$  oligomers can disrupt endosome vesicles and interfere with the retrograde transport of brain-derived neurotrophic factors, downregulating ubiquitin C-terminal hydrolase L1 (UCH-L1) and deubiquitinating enzymes, interfering with proteolysis (Poon et al., 2013).  $A\beta_{42}$  and  $A\beta_{40}$  oligomers can undergo intercellular transfer through the endosomal transport system and are highly metastatic with  $A\beta_{42}$  (Domert et al., 2014). Since  $A\beta$  oligomers are in the dynamic equilibrium of continuous

formation and degradation, there is no authoritative literature report on the content and presence of various oligomers (Noguchi et al., 2009; Esparza et al., 2016). However, current studies suggest that  $A\beta_{42}$  hexamers and dodecamers are the most neurotoxic isoforms.

Accumulation of beta-amyloid protein ( $A\beta$ ) in the extracellular space of the brain has been hypothesized to be a culprit in the pathogenesis of AD. In this issue of *Neuron*, Cirrito et al. (2008) describe a series of experiments demonstrating that extracellular  $A\beta$  levels are directly modulated by neuronal and synaptic activity (Schroeder and Koo, 2005).

Possible mechanisms of  $A\beta$  cell delivery: (1) Secretory vesicle mechanism: promotes the transfer of  $A\beta$  from a neuron across the synapse or more distantly to other neurons, exerting its toxic effects (Candelario and Steindler, 2014). Several observations support the idea that some of the  $A\beta$  is released via exosomes (Rajendran et al., 2006). One study showed that tunneling nanotubes (TNTs) formed by various neuronal cell lines can mediate the transport of different forms of  $A\beta$  and that this transport is bidirectional, with different velocities in various cell lines (Rustom et al., 2004; Zhang et al., 2021). Amyloid- $\beta$  induced membrane damage by TNT (Dilna et al., 2021); (2) Release and uptake of  $A\beta$ :  $A\beta$  oligomers may be similar to Tau protein and  $\alpha$ -synuclein, leaking in the pre-synaptic or posterior space and being directly ingested by another neuron (Hampel et al., 2021). Uptake, degradation and release of  $A\beta$  are also



possible in inflammation-responsive cells of the CNS (Chung et al., 1999; Maler et al., 2009).

## The damage of amyloid-β oligomers and fibers to mitochondria

Neurons are highly dependent on mitochondria to produce energy, so mitochondrial damage has a great impact on neuronal function (Fang et al., 2019). Aβ oligomers and fibers can impair mitochondrial function by the way of oxidative phosphorylation, mitochondrial dynamics (transport, fission, and fusion), bioenergetics and mitochondrial phagocytosis (removal of damaged mitochondria by autophagy). Aβ binds metal ions (mainly  $\text{Cu}^{2+}$ ,  $\text{Fe}^{3+}$ ) to reduce the formation of reductants (mainly  $\text{Cu}^+$ ,  $\text{Fe}^{2+}$ ), resulting in lipid and protein peroxidation, which causes oxidative stress (Smith et al., 2007). Aβ, similar to other pore forming toxins, induces perforation of neuronal membranes and mitochondrial membrane causing an increase in membrane conductance, intracellular calcium influx. Aβ oligomers pores on the mitochondrial membrane, causing  $\text{Ca}^{2+}$  non-regulating influx, causing multiple  $\text{Ca}^{2+}$  signaling pathways to be disordered, leading to neuronal death (Lau et al., 2007). One study demonstrated that blocking the MCU complex (is the main pathway for mitochondrial  $\text{Ca}^{2+}$  influx) *in vivo* with Ru360—a specific blocker of the channel—prevented the mitochondrial  $\text{Ca}^{2+}$  uptake elicited by TgCM. Then they observed that Ru360 did not interfere with the rise in the

cytosolic  $\text{Ca}^{2+}$  induced by Aβ. These results suggest that MCU is required for the increase in mitochondrial  $\text{Ca}^{2+}$  induced by Aβ *in vivo*, and points to MCU as a potential target candidate for AD (Calvo-Rodriguez and Bacskai, 2020).

## Inflammatory damage caused by amyloid-β oligomers and fibers

A variety of inflammatory factors secreted by microglia activated by Aβ oligomers or fibers not only cause inflammatory damage to neurons, but also increase APP expression and Aβ deposition (Blasko et al., 2000; Perry et al., 2010). Activated microglia release high mobility group protein-1 (HMG1) to bind to Aβ to form oligomers, while HMG1 is positively fed back to microglia to reduce its Aβ scavenging capacity (Takata et al., 2003; Hickman et al., 2008). Apoptosis-associated speck-like protein containing a C-terminal caspase activation and recruitment domain (ASC) spots released by microglia can rapidly bind to Aβ, increasing the formation of Aβ oligomers and Aβ aggregation (Venegas et al., 2017; Hulse and Bhaskar, 2022). Some studies found the nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is activated by glycolytic enzymes (Hughes and O'Neill, 2018); activation of the NLRP3 inflammasome has been demonstrated to contribute to AD pathology (Ising et al., 2019). However, there is no consensus on the difference in the effects of Aβ<sub>42</sub> or Aβ<sub>40</sub> on microglia. In addition, activated microglia can mediate

tau hyperphosphorylation via Toll-like receptor 4 and IL-1 receptors (Bhaskar et al., 2010).

## Loss of amyloid- $\beta$ physiological effects

Overexpression of A $\beta$  and APP are very important pathological proteins in AD, but A $\beta$  and APP have some physiological functions under normal circumstances (Pearson and Peers, 2006; Puzzo et al., 2008). APP is a transmembrane glycoprotein that plays an important role in neurogenesis, cellular stress, synaptic function, and plasticity. Soluble APP $\alpha$  mediates voltage-gated calcium channels to maintain calcium homeostasis under stress conditions. A $\beta$  generated under physiological conditions can enhance synaptic activation efficiency and plasticity (Kim et al., 2013; Li et al., 2013), and its generation is directly proportional to neuronal activity (Cirrito et al., 2008). A $\beta$  can bind and transport cholesterol and participate in lipid regulation (Umeda et al., 2010). Soluble A $\beta$  has a physiological role in regulating synaptic function and promoting neuronal growth and survival (Puzzo et al., 2015). There is evidence that A $\beta$  protects the brain from infection, repairs blood–brain barrier (BBB) leakage, promotes damage recovery and regulates synaptic function, and the cellular generation of A $\beta$  rapidly increases in response to a physiological challenge and often decreases on recovery (Yu et al., 2018). In the process of A $\beta$  oligomerization, fibrosis and deposition into amyloid plaques, soluble A $\beta$  loses its normal physiological function which may be one of the AD pathological mechanisms.

## Tau molecular structure and toxicity linked to amyloid- $\beta$

The neurofibrillary tangles formed by phosphorylated Tau are another important pathological marker of AD, but phosphorylated Tau is not all toxic, only the phosphorylation of specific residues AT180 (Tr231 and SR235) or 12E8 (Ser262 and Ser356) is pathologic, and phosphorylated Tau can reduce hippocampal excitability (Hatch et al., 2017). By analyzing the molecular structure of Tau, it was found that both tau and A $\beta$  are amyloid proteins and can form amyloid fibrils. Kadavath et al. (2015) used sNMR to find that Tau fiber residues 269–284 and 300–312 are in a hairpin conformation, which is markedly different from Tau on the microtubule. Further study found that Tau fibers interact with hydrophobic and polar bonds to form antiparallel and paired  $\beta$ -folds, and the N-terminal of the  $\beta$ -fold is formed by hexa-peptides 306–311 (VQVYK), which is essential for Tau polymerization into fibers (Xie et al., 2015). Fitzpatrick et al. (2017) used Cryo-EM to find that the various isomers of Tau were aggregated through the core region and the monomers were randomly added, Tau fiber adopts  $\beta$ -fold structure and is closed by G355.

Acetylation of Tau lysine residues (such as Lys174 and Lys280) inhibits tau degradation, impairs the interaction of tau with microtubules, promotes tau aggregation, and disrupts synaptic signaling (reduced KiBRA, a memory-related protein), leading to cognitive deficits (Min et al., 2010, 2015; Cohen et al., 2011; Irwin et al., 2012; Tracy et al., 2016). Studies on toxic effects have found that Tau, like A $\beta$ , exerts toxic effects primarily through forms. Tau oligomers can lead to electrophysiological damage and structural degradation of neurons, damage the function of microtubules or molecular motors and thus affect axon transport, and also cause intercellular transmission and corresponding changes of Tau protein in receptor neurons (Kopeikina et al., 2011; Calafate et al., 2015). On the other hand, Tau has also been found to have secondary nucleation. It has been found that the hexamer Tau has a strong ability to aggregate fibers (Jackson et al., 2016). In addition, Tau can also work with A $\beta$  to produce toxicity (Ittner et al., 2010). The hippocampus of tau knockout mice are resistant to ATP oligomer-induced LTP damage, indicating that Tau mediates the damage process of A $\beta$  to LTP (Li and Gotz, 2017; Puzzo et al., 2017). A $\beta$  oligomers form a complex with synaptic NMDA and mediate synaptic toxicity of tau via the CaMKK2-AMP kinase pathway (Mairet-Coello et al., 2013).

## Structure forms and generation, clearance of amyloid- $\beta$ in brain

In the brain, A $\beta$  is mainly generated by neurons and then secreted into the intercellular space. A $\beta$  is mostly secreted on the axon (pre-synaptic) and a little on the dendrites (post-synaptic). Astrocytes and microglia also generate small amounts of A $\beta$  (Wegiel et al., 2001; Niederst et al., 2015). The type of A $\beta$  in the brain is mainly A $\beta$ <sub>40</sub>, followed by A $\beta$ <sub>42</sub>.

Clearance of A $\beta$  in the brain is mainly extracellular and intracellular. Intracellular clearance is mainly degraded by enzymes in the intracellular proteasome and lysosome systems of neurons and glial cells (Guenette, 2003). Intracellular A $\beta$  is degraded by the ubiquitin-proteasome pathway, lysosomal cathepsin and autophagy pathways (Zhang et al., 2009; Querfurth and LaFerla, 2010; Perez et al., 2014). The intracellular degradation of A $\beta$  is affected by four major factors: enzyme expression and activity, ligand affinity and competition, cellular uptake capacity, and initiation of intracellular degradation pathways, all of which are found to be impaired in the context of AD (Wang et al., 2003; Lucin and Wyss-Coray, 2009). Deubiquitinase is one of the important A $\beta$  degradation pathways in neuron, and the A $\beta$  accumulation inhibits the deubiquitinase activity and affects A $\beta$  degradation (Zhang et al., 2018). Lysosomes contain hydrolytic enzymes that are capable of degrading A $\beta$ , whereas the hydrolytic machinery in AD are often overwhelmed. As the amount of A $\beta$  exceeds the lysosomal degradation ability, it will aggregate in the lysosome



or leak into the cytoplasm (Umeda et al., 2011; Gowrishankar et al., 2015). There are three types of autophagy, namely macroautophagy, microautophagy and chaperone-mediated autophagy, in which macroautophagy and chaperone-mediated autophagy dysfunction are associated with AD (Zare-Shahabadi et al., 2015). A large accumulation of A $\beta$ -rich unprocessed autophagic vacuoles was found in the neurites of AD, indicating significant impairment of autophagy degradation (Nixon, 2007; Boland et al., 2008). One study has suggested that defects in the autophagy-lysosomal pathway may even occur before A $\beta$  aggregation (Correia et al., 2015).

There are five main ways of extracellular clearance: First, A $\beta$  degrading by related enzymes. Animal experiments and clinical studies have suggested that serum A $\beta$  levels are elevated, enkephalinase (NEP) levels is decreased (Yasojima et al., 2001; Yin et al., 2006; Lim et al., 2011); Second, the phagocytic degradation of A $\beta$  glial cells. A $\beta$  in brain interstitial fluid (ISF) is phagocytized by microglia and astrocytes (Yoon and Jo, 2012); A $\beta$  plaques are degraded by microglia and astrocytes and degraded by the autophagy-lysosomal pathway (Cho et al., 2014; Morrone et al., 2015). It was found in AD that A $\beta$  phagocytized by glial cells was re-released extracellularly, indicating impaired phagocytic ability of glial cells (Nagele et al., 2003; Lee and Landreth, 2010). In AD, the increase in A $\beta$  degraded by the endosomal-lysosomal pathway leads to the accumulation of autophagic vacuoles and abnormal expansion of endosomes, leading to dysfunction of whole-cell proteasomes (Nixon and Cataldo, 2006; Chesser et al., 2013; Norambuena et al., 2018); Third, A $\beta$  transport in BBB. One study found that A $\beta$  generation rate did not differ between AD and control group, while the A $\beta$  clearance rate across the BBB decreased by 30%, indicating that the BBB changes play a role in AD (Mawuenyega et al., 2010). Low density lipoprotein receptor-related protein-1 (LRP1) is widely expressed in the BBB endothelial cells, and transports A $\beta$  in the brain to the plasma to play a role in clearing A $\beta$  in the brain (Erickson et al., 2012). Receptor for advanced glycation endproducts (RAGE) is a receptor on the BBB endothelial cells, which transports A $\beta$  in the plasma to the brain, which is normally low in expression levels (Chen et al., 2014). LRP1 and RAGE together regulate A $\beta$  transport in the BBB and maintain A $\beta$  balance in the brain. BBB damage may attenuate the expression of LRP1 and cause clearance of A $\beta$ , and may also increase the expression of RAGE, increase the A $\beta$  transported into the brain, and promote the progression of AD (Jaya Prasanthi et al., 2008; Zlokovic, 2011); Fourth, the blood cerebrospinal fluid barrier transport of A $\beta$ . In the case of AD, the expression of LRP1 and RAGE is completely opposite to that in the case of non-AD, which may be the compensation of the body for b BBB transport disorders (Johanson et al., 2008; Wraith and Nicholson, 2012; Gonzalez-Marrero et al., 2015); Fifth, astrocyte-mediated intracellular lymphatic system (ISF bulk flow). It was previously thought that this removal only accounted for about 10%, and it is now found that

its proportion may be higher (Iliff et al., 2012; Kress et al., 2014).

## Generation, structure form and clearance of amyloid- $\beta$ in blood circulation

### Generation and structure forms of amyloid- $\beta$ present in blood circulation

A $\beta_{40}$  and A $\beta_{42}$  in plasma are present in monomeric form and do not form fibers. Albumin, erythrocyte membrane proteins and other plasma molecules bind more than 90% of A $\beta$  monomers (Biere et al., 1996; Kuo et al., 1999, 2000a,b), while the half-life of unbound A $\beta_{40}$  and A $\beta_{42}$  is only 2.5–3 min in plasma (Ghiso et al., 2004). A $\beta_{40}$  accounts for about 80% of the total plasma A $\beta$ , and A $\beta_{42}$  accounts for less than 10% (Chen et al., 1995; Zheng et al., 2012). In the case of AD, the A $\beta$  monomer structure in plasma was found to change from a natural structure (random coil or  $\alpha$ -helix structure) to a  $\beta$ -sheet structure and it has been reported that the risk of AD can be assessed by detecting changes of A $\beta$  monomer structure in plasma (Nabers et al., 2016, 2018). APP<sub>751</sub> and APP<sub>695</sub> are abundantly expressed in platelets and 95% A $\beta$  in the plasma is derived from platelets (Sonkar et al., 2014). Peripheral tissue can also produce A $\beta$  into the plasma, affecting A $\beta$  level in the plasma (Kuo et al., 2000a,b).

### Clearance and structure forms of amyloid- $\beta$ in blood circulation

The A $\beta$  removal is mainly liver-based in the plasma, and more than 90% A $\beta$  is excreted into the bile by liver cells (Sehgal et al., 2012). The data obtained by the experiments showed that under normal conditions, the daily excretion of intact A $\beta$  in urine was less than 1% of the circulating pool (Ghiso et al., 1997).

#### Amyloid- $\beta$ monomer clearance in liver

Under normal conditions, the liver is the main organ of plasma A $\beta_{40}$  clearance. In a treatment study, it was found that the ability of the liver to clear A $\beta$  directly affects plasma A $\beta$  and intracerebral A $\beta$  levels. This study using *Withania somnifera* to treat AD found that *Withania somnifera* is an extract from plant roots that significantly increases the expression of LRP1 and NEP in the liver, the level of plasma LRP1 and the ability to bind A $\beta$ , thereby increasing the clearance of A $\beta$  in the brain. This suggests that in AD, the ability of the liver to clear A $\beta$  is reduced, which may affect A $\beta$  levels in the plasma and increase the risk of AD (Sehgal et al., 2012). Another study also confirmed

that LRP1 in the liver can mediate systemic clearance of A $\beta$ . In plasma, the soluble LRP1 is the major transporter of peripheral A $\beta$ . The soluble LRP1 forms a LRP1-A $\beta$  complex by binding of peripheral A $\beta$ , which reduces the concentration of A $\beta$  monomer in plasma, thereby inhibiting plasma free A $\beta$  monomer from re-entering the brain. In AD, LRP1 expression at the BBB is reduced, and the rupture of LRP1 in the circulation results in a decrease in its ability to bind to A $\beta$ . Cell surface LRP1 and circulating LRP1 are targets for drug therapy. Through lifestyle changes, statins can increase LRP1 expression in BBB and liver, and control the risk of AD (Sagare et al., 2012). It has been reported that because the liver has a strong ability to catabolize A $\beta$  and excrete into bile, it has little effect on plasma A $\beta$  levels in general liver function damage (Ghiso et al., 2004; Roher et al., 2009).

### Amyloid- $\beta$ monomer clearance in kidney

The kidney participates in the physiological metabolism of A $\beta$  by filtering A $\beta$  from the plasma to the urine. The A $\beta$  excreted by the kidneys is mainly soluble A $\beta$  monomer, because the oligomers and fibers have a large molecular weight and cannot pass through the glomerular filtration. Soluble A $\beta$  is a normal component of human urine, mainly A $\beta$ <sub>40</sub>. The kidney plays an important role in the peripheral clearance of A $\beta$ . A clinical study of chronic kidney disease (CKD) conditions explored the relationship between plasma A $\beta$  levels and cognitive decline, and the results showed that subjects with high plasma A $\beta$  levels had worse cognitive dysfunction scores than those with lower levels (Gronewold et al., 2017). According to the above studies, cognitive function decline in CKD is apparently due to increased plasma and brain A $\beta$  load. Another study found that plasma A $\beta$  levels (mainly A $\beta$ <sub>40</sub>) increased with the progression of CKD and were not affected by hemodialysis, suggesting that the kidney plays an important role in the peripheral clearance of A $\beta$ , and CKD increases the risk of cognitive impairment (Gronewold et al., 2016). At the same time, some studies suggest that hemodialysis can reduce plasma A $\beta$  levels during CKD (Liu et al., 2015). In the case of AD, elevated levels of A $\beta$  in the plasma may be associated with a progression of AD if accompanied by a renal clearance disorder of A $\beta$  caused by impaired renal function. Therefore, improving impaired renal function to reduce plasma A $\beta$  levels can be used as a strategy to prevent cognitive dysfunction.

### Links of amyloid- $\beta$ in the brain, plasma and peripheral tissues

There is a dynamic balance of A $\beta$  between the brain and plasma, mainly between soluble A $\beta$ . A $\beta$  in the plasma is almost always soluble, mainly monomer, but also some oligomers, but no fiber. A $\beta$  is generally considered to be soluble less than 20-mer and insoluble more than 20-mer. A $\beta$ <sub>40</sub> oligomers are

generally dimers, trimers, and tetramers, and A $\beta$ <sub>42</sub> oligomers can be dimers, trimers, and tetramers, even consisting of more than 1,000-mer. A $\beta$  in the plasma is mainly A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> is also present. Soluble A $\beta$  monomers and oligomers are also present in the brain, and soluble A $\beta$  oligomers form insoluble A $\beta$  oligomers, further forming A $\beta$  fibers, forming plaque deposits, which is one of the pathogenesis of AD.

Soluble A $\beta$  monomers and oligomers can communicate between the brain and plasma through various pathways such as *trans*-BBB transport and CSF. Under physiological conditions, A $\beta$  in the brain and plasma can exchange through the BBB. We have provided a clear evidence that, in a parabiosis model surgically fused an AD transgenic mouse with wild type mouse, the plasma A $\beta$  from a transgenic mouse can penetrate to the wild type mouse and cause AD-like pathology in the brain (Bu et al., 2018). Our studies suggest that plasma A $\beta$  is the important part of A $\beta$  pathogenic process of AD and peripheral clearance of A $\beta$  may be more favorable than the brain for the drug development targeting A $\beta$ . However, the amount of A $\beta$  transported from the brain into the plasma is greater than the amount of plasma transported into the brain. In the case of AD, it has been reported that the amount of A $\beta$  transported to the plasma in the brain is reduced by about 30% (Mawuenyega et al., 2010).

At present, there is still controversy about whether the total A $\beta$  level in the plasma rises or falls in the case of AD. One Study has compared plasma total A $\beta$ , A $\beta$ <sub>40</sub>, and A $\beta$ <sub>42</sub> levels in AD, mild cognitive impairment (MCI), and normal populations, and no statistically significant differences were found (Toledo et al., 2011). Plasma A $\beta$  biomarkers are closely related to CNS A $\beta$  status, but peripheral tissue has less effect on plasma A $\beta$ . Free plasma A $\beta$  is not a reliable biomarker for measuring the risk and diagnosis of AD. Plasma-soluble A $\beta$  do not reflect the deposition of brain A $\beta$ . This may be because soluble A $\beta$  in plasma is mainly produced by extracellular tissue cells (Lovheim et al., 2017).

A $\beta$ <sub>42</sub> is produced by the brain into the plasma, so the level of A $\beta$ <sub>42</sub> in the plasma can reflect the cross-BBB exchange of A $\beta$ . Most studies have concluded that plasma A $\beta$ <sub>42</sub> levels and plasma A $\beta$ <sub>42</sub>/A $\beta$ <sub>40</sub> ratios decrease (van Oijen et al., 2006). But another studies suggest that higher A $\beta$ <sub>42</sub> concentrations can significantly increase the risk of AD (Hansson et al., 2012; Hsu et al., 2017). In addition, other report found that there is no correlation between the concentration of soluble A $\beta$  in plasma and the occurrence of AD (Roher et al., 2009).

Since the detection of soluble A $\beta$  in plasma does not assess the development of AD, current research on plasma A $\beta$  has begun to shift to detect changes in its secondary structure (Nakamura et al., 2018). 15–20 years before the clinical symptoms of AD, the secondary structure of A $\beta$  changed from disordered or  $\alpha$ -helix to  $\beta$ -sheet enriched secondary structure. It was found that the change of secondary structure of A $\beta$  peptide is a reliable plasma in severe AD stage (Nabers et al., 2018).

Some experimental studies have found that peripheral clearance can reduce the concentration of A $\beta$  in the plasma,

and then guide the outflow of A $\beta$  in the brain through the dynamic balance, thereby reducing the deposition of A $\beta$  in the brain and improving cognitive function (Wang et al., 2017). In another study, intravenous NEP was used to increase plasma A $\beta$  clearance to see if it reduced brain A $\beta$  levels. It was found that plasma A $\beta$  levels in normal and AD mice decreased after 5 weeks treatment, but no significant decrease in A $\beta$  levels in the brain was found (Walker et al., 2013).

The above results demonstrate that the total amount of soluble A $\beta$  in the plasma is fluctuating and has no clear correlation with AD. We speculate that this is mainly because the plasma is dominated by A $\beta_{40}$ , which is mainly derived from the production of platelets and peripheral tissues, while the decrease in the amount of A $\beta_{40}$  transferred from the brain is not enough to have a significant impact on the plasma A $\beta_{40}$ . In addition, A $\beta_{42}$  in the plasma is mainly derived from the brain, and in the case of AD, the amount of A $\beta_{42}$  entering the plasma from the brain is reduced, and the level of A $\beta_{42}$  in the plasma is lowered. We speculate that there is no significant effect on the total amount of A $\beta$  in the plasma. On the other hand, at different stages of AD, the change of plasma A $\beta$  level is also fluctuating, so the relationship between A $\beta$  level in the plasma and AD may lead to different conclusions. We believe that this needs to be further studied in different stages of AD.

## Structure forms and toxicity of amyloid- $\beta$ and other diseases besides Alzheimer's disease

Amyloid- $\beta$  has attracted much attention for its association with over 30 illnesses (Harrison et al., 2007). Besides AD, A $\beta$  plays a crucial role in other brain disease like CAA and prion disorders, as well as systemic diseases such as osteoporosis and type 2 diabetes mellitus (T2DM). A $\beta$  can deposit in cerebral and peripheral tissues, and aggravate the pathological damage of these diseases, which are all thought to involve structure form changes of A $\beta$  proteins, such as  $\alpha$ -helix to  $\beta$ -sheet folding transition.

### Amyloid- $\beta$ and cerebral amyloid angiopathy

Cerebral amyloid angiopathy is cerebrovascular amyloid deposition, which the pathological changes of CAA are mainly the deposition of amyloid fibers on the middle and outer membrane of the small arteries and capillaries in the occipital and temporal cortex (Wang et al., 2000; Vinters, 2015). The classification of CAA is based on the type of

amyloid proteins deposited in the cerebral blood vessels, and A $\beta$ -CAA refers to one type of CAA that mainly deposits amyloid proteins as A $\beta$ . A $\beta$ -CAA is commonly found in elderly individuals and AD patients. Cerebrovascular A $\beta$  originates mainly from the brain and is transported to the vascular wall through a perivascular drainage pathway, where it polymerizes into fibrils on vascular basement membrane through interactions with extracellular components. A $\beta$  in the cerebrovascular is mainly A $\beta_{40}$ , and the severity of CAA correlate with the levels of soluble A $\beta_{40}$  in the brain. In the process of vascular A $\beta$  deposition, A $\beta_{42}$  is initially deposited, and later A $\beta_{40}$  is massively accumulated (Yamada and Naiki, 2012). In the past, the incidence of CAA was thought to be related to overproduction of A $\beta_{40}$ , a decrease of A $\beta$  degradation, or a decrease in A $\beta$  clearance due to impaired perivascular drainage. Recent study has found that A $\beta$  of CSF increases with normal aging, but both A $\beta_{40}$  and A $\beta_{42}$  of CSF decrease at CAA, which can be used as a biological marker of CAA. Reducing the production of A $\beta$  by inhibiting  $\beta$ -secretase at the early stage can prevent progression of CAA (Schelle et al., 2019). Study has observed that A $\beta$ -CAA occurs after intraperitoneal injection of A $\beta$  oligomers in mice and in some patients with traumatic brain injury. It is speculated that this may be related to A $\beta$  oligomers, which may be attached to metal surfaces and to resist conventional hospital sterilization. This suggests that the pathogenesis of A $\beta$ -CAA may be caused by A $\beta$  oligomers (Jaunmuktane et al., 2015). Further research found that mice with high expression of A $\beta_{40}$  did not find significant CAA pathology, whereas mice expressing A $\beta_{42}$  accumulate insoluble A $\beta_{42}$  and develop CAA. This suggests that the pathogenic oligomer of CAA is likely to be A $\beta_{42}$  oligomer, not A $\beta_{40}$  (McGowan et al., 2005; Watts et al., 2014). Amyloid peptides and proteins in review. Amyloid peptides and proteins in review. FXIIIa colocalizes with A $\beta$  in CAA which the ability of A $\beta_{42}$  to bind FXIIIa is greater than that of A $\beta_{40}$ , and that FXIIIa forms unique protein complexes with A $\beta$  that might play an important role in A $\beta$  deposition and persistence in the vessel wall (de Jager et al., 2016).

### Amyloid- $\beta$ and type 2 diabetes mellitus

Both T2DM and AD are associated with A $\beta$  deposition and insulin signal abnormalities during the pathogenesis. Insulin resistance is found in AD brains, especially in the cerebral cortex and hippocampus. This shows that AD is closely associated with T2DM. On the one hand, islet amyloid polypeptide (IAPP) is a hallmark feature of T2DM patients and involves pancreatic  $\beta$ -cell death (Montane et al., 2012). Studies have shown that IAPP deposition in the brain of AD patients is independent of

A $\beta$  (Jackson et al., 2013; Fawver et al., 2014). Inoculation of IAPP aggregation into AD mouse brain can aggravate AD pathology and memory impairment. Mice overexpressing human IAPP showed reduced exploratory behavior and impaired recognition memory, and a wide range of IAPP sediments and inflammatory markers were observed in their brain (Srodulski et al., 2014). The lack of IAPP mRNA in human brain indicates that the IAPP oligomer produced from pancreas enters the brain through blood circulation and promotes the accumulation (Jackson et al., 2013). IAPP oligomers can disrupt the membrane permeability of neurons, induce ROS, and alter Ca<sup>2+</sup> homeostasis and cell viability in astrocytes and neurons (Janson et al., 1999). Of particular interest is that IAPP has been found to have a typical  $\beta$ -sheet structure that can be aggregated alone or in combination with A $\beta$  to form oligomers or fibers. It has been demonstrated *in vitro* studies that IAPP accelerates A $\beta$  aggregation and the resulting fibers are composed of two peptides (Moreno-Gonzalez et al., 2017).

On the other hand, elevated plasma A $\beta$  levels accompanied by insulin resistance and subsequent deposition of A $\beta$  in the brain were found in AD mice, and the introduction of anti-A $\beta$  antibodies improved insulin sensitivity and glucose regulation (Zhang et al., 2012, 2013; Wijesekara et al., 2017). It was found in AD-T2DM transgenic mice that A $\beta$  can only be deposited in islets in the presence of IAPP. However, no A $\beta$  deposits were found in the islets of AD mice, and no A $\beta$  deposits were found in the islets of T2DM mice, indicating that the A $\beta$  deposits in the pancreas were not generated by pancreatic APP, but possibly from A $\beta$  in the blood circulation, and the accumulation of A $\beta$  in the pancreas was the result of cross-inoculation with IAPP (Wijesekara et al., 2017). A $\beta$  can competitively bind to insulin receptors and stimulate insulin resistance, and A $\beta$  has been shown to inhibit autophosphorylation of the insulin receptor and reduce insulin receptor levels and activity (Ling et al., 2002; Xie et al., 2002; Zhao et al., 2008; De Felice et al., 2009; Bomfim et al., 2012). In addition, A $\beta$  can induce the accumulation of reactive oxygen species, leading to damage to insulin signaling in peripheral tissues (Cai et al., 2015; Kim et al., 2017).

## Amyloid- $\beta$ and osteoporosis

Epidemiological studies have shown that bone density decreases and the incidence of fractures increases in AD patients, suggesting a link between the two diseases, but this phenomenon is rarely studied (Zhou et al., 2011). APP and A $\beta$  regulate osteoclast (OC) differentiation both *in vitro* and *in vivo*. In AD mice, OC differentiation has an age-dependent biphasic change. The increase in OC differentiation in young mice is mediated by A $\beta$  oligomers and RAGE receptors in bone marrow macrophages (BMMS); the decrease in OC differentiation in

aged rats may be due to an increase in soluble RAGE and osteoprotegerin, although the osteoclastic effect is reduced, but this reduces the ability of bone remodeling, thereby increasing the incidence of fracture without significant changes in bone density. This study suggests that APP/A $\beta$  and RAGE act as a common causative agent for AD and osteoporosis (Cui et al., 2011). In addition, another study demonstrated that elevated levels of A $\beta$ <sub>42</sub> play an important role in the pathogenesis of osteoporosis. The study found that mRNA and protein expression levels of A $\beta$ <sub>42</sub> and APP were significantly elevated in bone cells of osteoporosis patients and rat models, and showed a negative correlation with bone mineral density. A $\beta$ <sub>42</sub> is mainly located in the cytoplasmic membrane, cytoplasm and extracellular matrix, which can effectively promote osteoclast differentiation and activation, and abnormal deposition of A $\beta$  occurs in bone tissue. The study concluded that A $\beta$  may be a candidate biomarker for the identification of osteoporosis drug targets (Li et al., 2014).

## Molecular structure-based amyloid- $\beta$ therapeutic strategy

The current treatment for AD is aimed at clinical symptoms and does not control the progression of the disease. Links of A $\beta$  metabolism in the brain, plasma and peripheral tissues and possible targets for therapy are shown in Figure 7. Currently, cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists are the only clinically available options. A $\beta$  plaque is the main pathological feature of AD and is the basis of the amyloid cascade hypothesis. The accumulation of A $\beta$  in the brain is an important early factor in the pathogenesis of AD, which ultimately leads to neurodegeneration and dementia. At the present stage, designing drugs and treatments based on the type of A $\beta$  (A $\beta$ <sub>40</sub> or A $\beta$ <sub>42</sub>) and structural form (fiber, oligomer or monomer) by reducing the generation of A $\beta$ , increasing the clearance of A $\beta$ , or reducing the toxicity of A $\beta$  is the most important direction for the study of prevention and treatment strategies for AD (Table 1).

## Inhibiting $\beta$ -site amyloid precursor protein cleaving enzyme-1 to reduce Amyloid- $\beta$ generation

$\beta$ -site amyloid precursor protein cleaving enzyme-1 (BACE1) is an essential cleavage enzyme in the process of APP to generate A $\beta$ , and inhibition of BACE1 directly affects AD pathological process. Several years ago, a number of different structurally selective BACE1 inhibitors have been designed and entered the clinical evaluation trial phase (De Strooper et al., 2010; Sambamurti et al., 2011; Yan and Vassar, 2014). Two BACE inhibitors have recently been reported to worsen



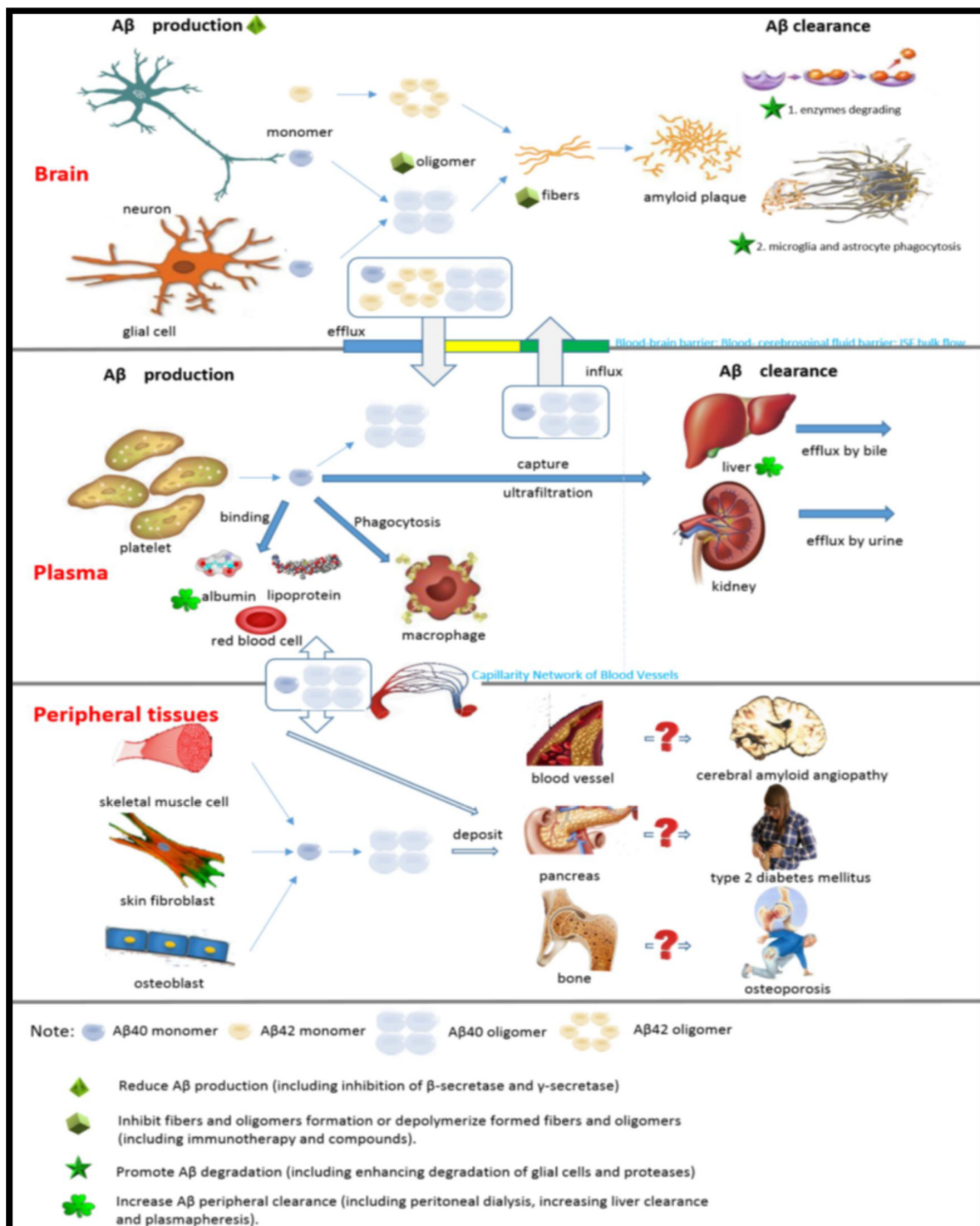


FIGURE 7  
Links of Aβ metabolism in the brain, plasma and peripheral tissues and possible targets for therapy.

cognitive function during clinical trials. In atabecestat trial, a BACE inhibitor, Henley et al. (2019) found that subjects experienced worse cognitive function and frequent adverse

events such as anxiety, sleep, dreams and depression. Egan et al. (2018, 2019) found that verubecestat worsened cognitive function in another drug trial. Although verubecestat found a

TABLE 1 Therapeutic strategy based on A $\beta$  molecular structure.

Name	Experimental research or clinical trial	Therapeutic strategy for the protein structure of AD	References
1. BACE1 inhibitors	<p><b>Clinical trial</b> That subjects experienced worsen cognitive function and adverse events (anxiety, sleep, dreams and depression).</p> <p><b>Clinical trial</b> Elenbecestat and umibecestat are still in clinical trials, and have not been found to cause serious cognitive problems.</p>	BACE1 inhibitors: inhibiting the process of APP to generate A $\beta$	<p>Henley et al., 2019</p> <p>Selkoe, 2019</p>
2. $\gamma$ -secretase inhibitor (GSI)	<p><b>Experimental research</b> GSI can not only reduce the generation of A<math>\beta</math>, but also significantly reduce the expression of APP.</p> <p><b>Experimental research</b> GSI inhibited <math>\beta</math>-sheet aggregation and increasing its ability to decompose, reducing caspase-3 and -9 activity.</p> <p><b>Clinical trial</b> The phase III clinical trial of Semagacestat found that some effects.</p>	GSI: Decreasing A $\beta$ generation	<p>Law et al., 2018</p> <p>Carmona et al., 2020</p> <p>Tagami et al., 2017</p>
3. Treatment of oligomer	<p><b>Experimental research</b> Phenolic compounds have been found that it can inhibit the oligomerization of A<math>\beta_{40}</math> and A<math>\beta_{42}</math>.</p> <p><b>Experimental research</b> A<math>\beta_{42}</math> oligomer antagonists might promote oligomer conversion or depolymerization.</p>	Promoting oligomer conversion or depolymerization	<p>Ladiwala et al., 2011</p> <p>Sinha et al., 2011</p>
4. Degrading A $\beta$	<p><b>Experimental research</b> Serotonin precursors and their derivatives reduced the A<math>\beta</math> level in the brain of APP/PS1 mice by regulating NEP and improved the memory of mice.</p> <p><b>Experimental research</b> Use of RGFP-966 (a brain-penetrant and selective HDAC3 inhibitor) increased plasma levels of NEP, decreased A<math>\beta</math> at brain and peripheral levels, and improved spatial learning and memory.</p>	Promoting the proteases and glial cells to degrade A $\beta$	<p>Klein et al., 2018</p> <p>Janczura et al., 2018</p>
5. Immunotherapy for A $\beta$	<p><b>Experimental research</b> Studies in AD mice have shown that solanezumab primarily recognizes soluble A<math>\beta</math> monomers and binds to A<math>\beta</math> plaques when used in large doses.</p> <p><b>Clinical trial</b> In a phase II clinical study of AD patients, solanezumab increased the total A<math>\beta_{40}</math> and A<math>\beta_{42}</math> levels in the plasma and CSF of patients, but did not improve the score of the ADAS-Cog14 cognitive scale in phase III trials.</p>	Immunotherapy for A $\beta$ structural forms, including A $\beta$ monomers, oligomers, and fibers	<p>Bouter et al., 2015</p> <p>Honig et al., 2018</p> <p>Doody et al., 2014</p>
6. A $\beta$ monomer clearance in plasma	<p><b>Experimental research</b> Intramuscular delivery of p75NTR ectodomain in the brain of AD mice reversed the behavioral deficits and AD pathologies.</p> <p><b>Experimental research</b> Experiments in AD mice have found that multifunctional magnetite/ceria nanoparticle assemblies reduces A<math>\beta</math> levels in the plasma and brain, and also prevents the spatial working memory deficits.</p>	A $\beta$ clearance in peritoneal dialysis	<p>Yao et al., 2015</p> <p>Wang et al., 2016</p> <p>Kim et al., 2019</p>

BACE1,  $\beta$ -site amyloid precursor protein cleaving enzyme-1; GSI,  $\gamma$ -secretase inhibitor.

decrease in A $\beta$  of CSF and brain in previous tests, it did not find an effect on cognitive function, and found that verubecestat increased the adverse events incidence including anxiety, sleep disorders and depression. For safety, long-term inhibition of this A $\beta$ -producing protease requires the design of more selective drug candidates. Two another BACE inhibitors (elenbecestat and umibecestat) that are still in clinical trials have not been found to cause serious cognitive problems (Selkoe, 2019).

## Inhibiting $\gamma$ -secretase to reduce amyloid- $\beta$ generation

The  $\gamma$ -secretase inhibitor (GSI) is a drug that reduces the generation of A $\beta$  by inhibiting  $\gamma$  cleavage in the App membrane. The generation of A $\beta$  requires the cleavage of  $\gamma$ -secretase, so  $\gamma$ -secretase is involved in the pathogenesis of AD and is one of the targets for targeting A $\beta$  treatment (De Strooper and Chavez Gutierrez, 2015). Although some clinical trials have stopped due to lack of clinical efficacy or side effects, animal studies for it are still in progress.

Studies have shown that GSI can not only reduce the generation of A $\beta$ , but also significantly reduce the expression of APP (Law et al., 2018). Another study explored the role of flavonols (mulberry and isoquercetin) and flavanones (hesperidin and neohesperidin) as GSIs, inhibiting  $\beta$ -sheet aggregation and increasing its ability to decompose, reducing caspase-3 and -9 activity (Carmona et al., 2020). Presenilin is a catalytic component of  $\gamma$ -secretase. Studies have investigated whether  $\gamma$ -secretase specificity to substrates in mouse cells expressing human PS1 or PS2 in coordination with PS1 or PS2. As a result, it was found that mouse PS1 plays a major role in  $\gamma$ -secretase cleavage of APP and Notch as compared with mouse PS2. GSI blocks PS2- $\gamma$  secretase in mice better than PS1- $\gamma$  secretase, while GSI preferentially targets human PS1- but not PS2-dependent  $\gamma$ -secretase activity (Stanga et al., 2018). Therefore, we should pay attention to these differences when designing GSI and reduce side effects. A study of the causes of failure in the phase III clinical trial of Semagacestat found that some Semagacestat effects were significantly different from those caused by loss of presenilin function. Therefore, Semagacestat may be a pseudo-GSI, and its clinical trials did not really validate the effectiveness of  $\gamma$ -secretase as a strategy for the treatment of A $\beta$  (Tagami et al., 2017). Surprisingly, recent *in vitro* studies have found that low doses of GSI may increase A $\beta$  generation. Low doses of DAPT (a GSI) increased the generation of several A $\beta$  peptides, particularly A $\beta_{x-42}$ , and increased A $\beta$  oligomers were found in cortical neurons treated with low doses of DAPT (Agholme et al., 2017). Other studies have found rebound effects caused by GSI, such as increased levels of PS1 and other  $\gamma$ -secretase subunits. After the treatment of primary neurons with DAPT or avagacestat (a kind of GSI), the expression of PS1 was

significantly increased. After 21 days of taking avagacestat, the expression of PS1 in the brain increased. Long-term taking of avagacestat increased the anxiety-like behaviors in rats (Ono et al., 2012).

## Promoting oligomer conversion or depolymerization

A large number of studies have shown that oligomers are the most toxic species, but it is not clear whether oligomers can be treated as a selective therapeutic target and be remodeled into non-toxic or low-toxic structures with drugs. At present, there are many researches on drug-targeting oligomers and some progress has been made. Studies on phenolic compounds have found that it can inhibit the oligomerization of A $\beta_{40}$  and A $\beta_{42}$ , and even the aggregation of A $\beta$  fibers by binding specific amino acid residues on A $\beta$  monomers (Ladiwala et al., 2011). Another study evaluated the conformation specificity and remodeling pathways of small aromatic molecules to A $\beta_{42}$  oligomers and classified them into class I, II, and III molecules according to the different pathways of A $\beta_{42}$  oligomer antagonists. Class I molecules remodel A $\beta$  oligomers into non-toxic large non-pathway oligomers; Class II molecules convert A $\beta$  oligomers into fibers, but do not decompose A $\beta$  fibers; Class III molecules degrade A $\beta$  oligomers and fibers into non-toxic low-molecular substances (Sinha et al., 2011).

Amyloid- $\beta$  is primarily a pathogenic protein characterized by its own misfolding and aggregation. Therefore, inhibition or regulation of abnormal protein self-folding and aggregation is an effective strategy for preventing and treating A $\beta$ . The study found that a lead compound called CLR01 (Lys specific molecular tweezers) can inhibit the aggregation and toxicity of A $\beta$  by binding to Lys residues, which can destroy the hydrophobic and electrostatic effects that play an important role in the nucleation process, oligomerization and fiber extension of A $\beta$  (Knight et al., 2013; Scheidt et al., 2019).

Once the A $\beta_{42}$  fiber is produced, it can continuously catalyze the formation of new A $\beta$  oligomers on the surface of its fibers through a secondary nucleation mechanism. Recently, Cohen demonstrated *in vitro* that Brichos redirects secondary nucleation to a pathway that forms the least toxic oligomer by binding to the surface of A $\beta$  fibers. This suggests that molecular chaperones can reduce the toxic effects of A $\beta$  by selectively inhibiting secondary nucleation of A $\beta$  (Sinha et al., 2011).

A study by synthesizing a novel cobalt (III) Schiff base complex with a methylamine axial ligand found that it can reduce the formation of  $\beta$ -sheets, destabilize preformed  $\beta$ -sheets and suppress aggregation. This indicates that the Cobalt complex is also a candidate drug targeting A $\beta$  aggregation (Iscen et al., 2019).

## Promoting proteases and glial cells to degrade amyloid- $\beta$

Enkephalinase (NEP) is an important catalytic enzyme for the degradation of A $\beta$  monomers and non-pathway oligomers in the brain (Kanemitsu et al., 2003). The expression and activity of NEP is significantly reduced in AD mice and patients, so maintaining and increasing the expression and activity of NEP is a potential strategy for the prevention and treatment of A $\beta$  disease (Bourassa et al., 2019). One study has shown that serotonin precursors and their derivatives reduce the A $\beta$  level in the brain of APP/PS1 mice by regulating NEP and improve the memory of mice (Klein et al., 2018). Another study demonstrated in the AD mouse model that the use of RGFP-966 (a brain-penetrant and selective HDAC3 inhibitor) increased plasma levels of NEP, decreased A $\beta$  at brain and peripheral levels, and improved spatial learning and memory (Janczura et al., 2018). The above research provides us with new treatment ideas.

In addition, a study has found that the ubiquitin-proteasome proteolytic pathway can degrade APP, thereby reducing A $\beta$  generation (Jung et al., 2015). Another study found that the proteasome disorder involves the UCH-L1, whose mRNA levels are reduced in the hippocampus of the AD brain. A $\beta$  downregulates UCH-L1 in AD brain, which in turn impairs BDNF/TRKB-mediated retrograde signaling, impairing synaptic plasticity and neuronal survival. Therefore, inhibition of A $\beta$  downregulation of UCH-L1, protection of synaptic plasticity and neuronal physiological function is one of the therapeutic strategies that can be explored (Poon et al., 2013).

The study found that Sodium ludin (NaR) not only increased microglia clearance of A $\beta$  by increasing the expression of receptors associated with microglia phagocytosis, but also promoted the transition from anaerobic glycolysis to mitochondrial oxidative phosphorylation, providing microglia with sufficient energy to clear A $\beta$ . Thus, NaR can reduce neuroinflammation, enhance A $\beta$  clearance, reduce synaptic plasticity damage, and reverse spatial learning and memory impairment. This suggests that NaR is a potential therapeutic agent for AD (Pan et al., 2019).

## Immunotherapy for different amyloid- $\beta$ structural forms

Immunotherapy for A $\beta$  has been a research hotspot, although great progress has been made, it is far from meeting the needs of clinical application. Early immunotherapy was simply targeting A $\beta$  without distinguishing between different structural forms, leading to reduced levels of A $\beta$  in the brain but no improvement in cognitive dysfunction in AD mice and patients, or serious side effects. Targets of current immunotherapeutic research have turned to specific toxic A $\beta$  structural forms,

including A $\beta$  monomers, oligomers, and fibers. The antibody targeting A $\beta$  monomer currently under investigation is mainly Solanezumab, a humanized, IgG1 monoclonal antibody that targets the A $\beta$ <sub>13–28</sub> amino acid residue sequence. Studies in AD mice have shown that solanezumab primarily recognizes soluble A $\beta$  monomers and binds to A $\beta$  plaques when used in large doses (Bouter et al., 2015). In a phase II clinical study of AD patients, solanezumab increased the total A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> levels in the plasma and CSF of patients, but did not improve the score of the ADAS-Cog14 cognitive scale in phase III trials (Doody et al., 2014; Honig et al., 2018). The toxicity of A $\beta$  oligomers has the strongest evidence supported by a large number of studies, so monoclonal antibodies targeting A $\beta$  oligomers are a research hotspot of immunotherapy. Crenezumab is a humanized anti-A $\beta$  monoclonal IgG4, which has a strong affinity for the pentamers and hexamers of A $\beta$ . Injection of Crenezumab into the brain of mice does not cause significant inflammatory changes in the brain of AD mice. However, no significant improvement in cognitive impairment was observed (Fuller et al., 2015; Zhao et al., 2017). In a small sample of clinical studies, it was found that Crenezumab can improve cognitive impairment in patients with mild AD (Cummings et al., 2018). CAD106 is an active immunization vaccine consisting of multiple copies of A $\beta$  1–6 amino acid residues coupled to an adjuvant carrier. The antibody induced by CAD106 mainly binds to the oligomers and monomers of A $\beta$  and blocks its toxicity, and has obvious adverse reactions. However, it does not improve the behavioral or cognitive dysfunction in patients with AD, suggesting that CAD106 is not effective in the treatment of AD (Winblad et al., 2012; Vandenberghe et al., 2017).

Still other monoclonal antibodies target both A $\beta$  oligomers and fibrous structures such as Gantenerumab and Aducanumab. Gantenerumab is a monoclonal IgG1 antibody that binds to the amino terminus and central region of A $\beta$ . It is found in AD mice to have a much higher affinity for A $\beta$  oligomers and fibers than monomers and to reduce A $\beta$  plaques in the cerebral cortex (Bohmann et al., 2012). Aducanumab is a recombinant human IgG1 antibody that recognizes the A $\beta$  3–7 amino acid residue sequence, mainly binding to A $\beta$  oligomers and fibers. The study found that Aducanumab can reduce the size of A $\beta$  plaque in the brain of young mice, but has no significant effect on A $\beta$  plaques in the brain of aged mice and AD patients, Aducanumab can reduce A $\beta$  load in the brain and demonstrates an improvement in cognitive and clinical function for the first time in a dose- and time-dependent manner (Sevigny et al., 2017).

## Therapeutic strategy for amyloid- $\beta$ monomer clearance in plasma

A study has observed whether peritoneal dialysis can reduce the pathological characteristics and cognitive impairment of AD, and the results showed that peritoneal dialysis reduced



the A $\beta$  level of plasma and brain inter-tissue fluid and A $\beta$  deposition, and improved the behavioral defects of AD mice (Jin et al., 2017). This suggests that peritoneal dialysis is a method of treatment for AD.

Neurotrophin receptor p75 (p75NTR) mediates A $\beta$ -induced neurodegenerative signals, and its extracellular domain (p75ECD) is a physiological protective factor against A $\beta$  in AD. p75ECD is significantly reduced in brain tissue and CSF in AD patients and mice. Intramuscular delivery of p75NTR ectodomain before or after A $\beta$  deposition in the brain of AD mice reversed the behavioral deficits and AD pathologies, such as A $\beta$  deposit, Tau phosphorylation and suppressing  $\beta$ -secretase expression and activities. Peripheral administration of p75ECD represents a promising strategy for AD treatment (Yao et al., 2015; Wang et al., 2016).

Plasma albumin inhibited the growth of A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> fibers, delayed the formation of fibers, and reduced the total amount of fibers (Stanyon and Viles, 2012). In 2009, a small sample of patients with mild-to-moderate AD was followed up for 1 year. The results showed that plasma A $\beta$  levels were correlated with plasmapheresis, and their cognitive scores were stable during the 1-year follow-up (Boada et al., 2009).

However, the efficacy of this approach may be affected by BBB's effect on the transport of A $\beta$  in the brain and the entry of A $\beta$  produced by other organs into the serum. The influx of ISF into CSF is another major pathway of A $\beta$  clearance. Although the concentration of albumin in CSF is much lower than that in plasma, CSF mixing with ISF is not hindered by the highly selective barrier and A $\beta$  in CSF is not directly exchanged with the peripheral A $\beta$ , so A $\beta$  in the two pools is more directly exchanged. Albumin replacement in CSF can be used as an alternative to clearing A $\beta$  in the brain (Menendez-Gonzalez and Gasparovic, 2019).

Amyloid- $\beta$  can be captured by erythrocyte immune adhesion and subject to complement-mediated clearance from the peripheral circulation, but these mechanisms are deficient in AD. A $\beta$  dose-dependently activated serum complement. Studies have found that binding of antibodies to A $\beta$  can significantly increase the activation and opsonization of complement, and subsequently enhance the capture of A $\beta$  by red blood cells and macrophages, and promote the peripheral clearance of A $\beta$ . This indicates that it is a viable pathway for peripheral clearance of A $\beta$  (Brubaker et al., 2017; Crane et al., 2018).

A new extracorporeal A $\beta$  cleansing system, multifunctional magnetite/ceria nanoparticle assemblies, can remove A $\beta$  from the plasma its reactive oxygen species. Experiments in transgenic mice have found that it reduces A $\beta$  levels in the plasma and brain, and also prevents the spatial working memory deficits, suggesting that the method can be used for AD prevention and therapy (Kim et al., 2019).

Alzheimer's disease patients are often accompanied by vascular risk factors and experimental studies have shown that

hypertension, diabetes, and high cholesterol can increase A $\beta$  deposition in the brain (Li et al., 2011; Zhu et al., 2014; van der Kant et al., 2019). In several prospective clinical studies in China, 837 patients with MCI have demonstrated that controlling vascular risk factors can prevent AD (Li et al., 2011). In patients with vascular risk factors, controlling vascular risk factors can reduce the risk of AD (Jiao et al., 2015).

## Conclusion

Hardy and Higgins (1992) proposed AD the pathogenic mechanism of protein cascade hypothesis, A $\beta$  has become the most popular molecule in AD research. A large number of studies have been done on the specific pathogenesis of A $\beta$ , which has a profound understanding of the pathogenesis of AD, but it has not yet fully revealed the pathogenesis caused by A $\beta$ . With the development of structural biology technologies such as sNMR and Cryo-EM, the molecular structure of A $\beta$  has been analyzed at the atomic level, which provides a new and more refined perspective for understanding the role of A $\beta$  in the pathogenesis of AD and developing disease-modifying drugs by targeting A $\beta$ .

## Author contributions

HY and JL developed the review's concept and structure and contributed to writing this review. XL, LM, and MH participated in some of the writing. HZ and RZ revised and finalized the review. All authors read and approved the final manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## References

- Agholme, L., Clarin, M., Gkanatsiou, E., Kettunen, P., Chebli, J., Brinkmalm, G., et al. (2017). Low-dose gamma-secretase inhibition increases secretion of Abeta peptides and intracellular oligomeric Abeta. *Mol. Cell. Neurosci.* 85, 211–219. doi: 10.1016/j.mcn.2017.10.009
- Area-Gomez, E., de Groof, A. J., Boldogh, I., Bird, T. D., Gibson, G. E., Koehler, C. M., et al. (2009). Presenilins are enriched in endoplasmic reticulum membranes associated with mitochondria. *Am. J. Pathol.* 175, 1810–1816. doi: 10.2353/ajpath.2009.090219
- Area-Gomez, E., Del Carmen Lara Castillo, M., Tambini, M. D., Guardia-Laguarta, C., de Groof, A. J., Madra, M., et al. (2012). Upregulated function of mitochondria-associated ER membranes in Alzheimer disease. *EMBO J.* 31, 4106–4123. doi: 10.1038/emboj.2012.202
- Bateman, R. J., Mawuenyega, K. G., and Wildburger, N. C. (2019). The structure of amyloid-beta dimers in Alzheimer's disease brain: A step forward for oligomers. *Brain* 142, 1168–1169. doi: 10.1093/brain/awz082
- Bernstein, S. L., Dupuis, N. F., Lazo, N. D., Wyttenbach, T., Condrón, M. M., Bitan, G., et al. (2009). Amyloid-beta protein oligomerization and the importance of tetramers and dodecamers in the aetiology of Alzheimer's disease. *Nat. Chem.* 1, 326–331. doi: 10.1038/nchem.247
- Bertini, I., Gonnelli, L., Luchinat, C., Mao, J., and Nesi, A. (2011). A new structural model of Abeta40 fibrils. *J. Am. Chem. Soc.* 133, 16013–16022. doi: 10.1021/ja2035859
- Bhaskar, K., Konerth, M., Kokiko-Cochran, O. N., Cardona, A., Ransohoff, R. M., and Lamb, B. T. (2010). Regulation of tau pathology by the microglial fractalkine receptor. *Neuron* 68, 19–31. doi: 10.1016/j.neuron.2010.08.023
- Biere, A. L., Ostaszewski, B., Stimson, E. R., Hyman, B. T., Maggio, J. E., and Selkoe, D. J. (1996). Amyloid beta-peptide is transported on lipoproteins and albumin in human plasma. *J. Biol. Chem.* 271, 32916–32922. doi: 10.1074/jbc.271.51.32916
- Bitan, G., Kirkitadze, M. D., Lomakin, A., Vollers, S. S., Benedek, G. B., and Teplow, D. B. (2003). Amyloid beta -protein (Abeta) assembly: A beta 40 and Abeta 42 oligomerize through distinct pathways. *Proc. Natl. Acad. Sci. U. S. A.* 100, 330–335. doi: 10.1073/pnas.222681699
- Blasko, I., Veerhuis, R., Stampfer-Kountchev, M., Saurwein-Teissl, M., Eikelenboom, P., and Grubeck-Loebenstein, B. (2000). Costimulatory effects of interferon-gamma and interleukin-1beta or tumor necrosis factor alpha on the synthesis of Abeta1-40 and Abeta1-42 by human astrocytes. *Neurobiol. Dis.* 7, 682–689. doi: 10.1006/nbdi.2000.0321
- Boada, M., Ortiz, P., Anaya, F., Hernández, I., Muñoz, J., Núñez, L., et al. (2009). Amyloid-targeted therapeutics in Alzheimer's disease: Use of human albumin in plasma exchange as a novel approach for Abeta mobilization. *Drug News Perspect.* 22, 325–339. doi: 10.1358/dnp.2009.22.6.1395256
- Bohrmann, B., Baumann, K., Benz, J., Gerber, F., Huber, W., Knoflach, F., et al. (2012). Gantenerumab: A novel human anti-Abeta antibody demonstrates sustained cerebral amyloid-beta binding and elicits cell-mediated removal of human amyloid-beta. *J. Alzheimers Dis.* 28, 49–69. doi: 10.3233/jad-2011-110977
- Boland, B., Kumar, A., Lee, S., Platt, F. M., Wegiel, J., Yu, W. H., et al. (2008). Autophagy induction and autophagosome clearance in neurons: Relationship to autophagic pathology in Alzheimer's disease. *J. Neurosci.* 28, 6926–6937. doi: 10.1523/jneurosci.0800-08.2008
- Bomfim, T. R., Forny-Germano, L., Sathler, L. B., Brito-Moreira, J., Houzel, J. C., Decker, H., et al. (2012). An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Abeta oligomers. *J. Clin. Invest.* 122, 1339–1353. doi: 10.1172/jci57256
- Bourassa, P., Tremblay, C., Schneider, J. A., Bennett, D. A., and Calon, F. (2019). Beta-amyloid pathology in human brain microvessel extracts from the parietal cortex: Relation with cerebral amyloid angiopathy and Alzheimer's disease. *Acta Neuropathol.* 137, 801–823. doi: 10.1007/s00401-019-01967-4
- Bouter, Y., Lopez Nogueroles, J. S., Tucholla, P., Crespi, G. A., Parker, M. W., Wiltfang, J., et al. (2015). Abeta targets of the biosimilar antibodies of Bapineuzumab, Crenezumab, Solanezumab in comparison to an antibody against Ntruncated Abeta in sporadic Alzheimer disease cases and mouse models. *Acta Neuropathol.* 130, 713–729. doi: 10.1007/s00401-015-1489-x
- Brubaker, W. D., Crane, A., Johansson, J. U., Yen, K., Garfinkel, K., Mastroeni, D., et al. (2017). Peripheral complement interactions with amyloid beta peptide: Erythrocyte clearance mechanisms. *Alzheimers Dement* 13, 1397–1409. doi: 10.1016/j.jalz.2017.03.010
- Bu, X. L., Xiang, Y., Jin, W. S., Wang, J., Shen, L. L., Huang, Z. L., et al. (2018). Blood-derived amyloid-beta protein induces Alzheimer's disease pathologies. *Mol. Psychiatr.* 23, 1948–1956. doi: 10.1038/mp.2017.204
- Cai, Z., Xiao, M., Chang, L., and Yan, L. J. (2015). Role of insulin resistance in Alzheimer's disease. *Metab. Brain Dis.* 30, 839–851. doi: 10.1007/s11011-014-9631-3
- Calafate, S., Buist, A., Miskiewicz, K., Vijayan, V., Daneels, G., de Strooper, B., et al. (2015). Synaptic Contacts Enhance Cell-to-Cell Tau Pathology Propagation. *Cell Rep.* 11, 1176–1183. doi: 10.1016/j.celrep.2015.04.043
- Calvo-Rodriguez, M., and Bacskaï, B. J. (2020). High mitochondrial calcium levels precede neuronal death in vivo in Alzheimer's disease. *Cell Stress* 4, 187–190. doi: 10.15698/cst2020.07.226
- Candelario, K. M., and Steindler, D. A. (2014). The role of extracellular vesicles in the progression of neurodegenerative disease and cancer. *Trends Mol. Med.* 20, 368–374. doi: 10.1016/j.molmed.2014.04.003
- Carmona, V., Martín-Aragón, S., Goldberg, J., Schubert, D., and Bermejo-Bescos, P. (2020). Several targets involved in Alzheimer's disease amyloidogenesis are affected by morin and isoquercitrin. *Nutr. Neurosci.* 23, 575–590. doi: 10.1080/1028415x.2018.1534793
- Chen, C., Li, X. H., Tu, Y., Sun, H. T., Liang, H. Q., Cheng, S. X., et al. (2014). Abeta-AGE aggravates cognitive deficit in rats via RAGE pathway. *Neuroscience* 257, 1–10. doi: 10.1016/j.neuroscience.2013.10.056
- Chen, M., Inestrosa, N. C., Ross, G. S., and Fernandez, H. L. (1995). Platelets are the primary source of amyloid beta-peptide in human blood. *Biochem. Biophys. Res. Commun.* 213, 96–103. doi: 10.1006/bbrc.1995.2103
- Chen, Y. R., and Glabe, C. G. (2006). Distinct early folding and aggregation properties of Alzheimer amyloid-beta peptides Abeta40 and Abeta42: Stable trimer or tetramer formation by Abeta42. *J. Biol. Chem.* 281, 24414–24422. doi: 10.1074/jbc.M602363200
- Chesser, A. S., Pritchard, S. M., and Johnson, G. V. (2013). Tau clearance mechanisms and their possible role in the pathogenesis of Alzheimer disease. *Front. Neurol.* 4:122. doi: 10.3389/fneur.2013.00122
- Cho, M. H., Cho, K., Kang, H. J., Jeon, E. Y., Kim, H. S., Kwon, H. J., et al. (2014). Autophagy in microglia degrades extracellular beta-amyloid fibrils and regulates the NLRP3 inflammasome. *Autophagy* 10, 1761–1775. doi: 10.4161/auto.29647
- Chung, H., Brazil, M. I., Soe, T. T., and Maxfield, F. R. (1999). Uptake, degradation, and release of fibrillar and soluble forms of Alzheimer's amyloid beta-peptide by microglial cells. *J. Biol. Chem.* 274, 32301–32308. doi: 10.1074/jbc.274.45.32301
- Cirrito, J. R., Kang, J. E., Lee, J., Stewart, F. R., Verges, D. K., Silverio, L. M., et al. (2008). Endocytosis is required for synaptic activity-dependent release of amyloid-beta in vivo. *Neuron* 58, 42–51. doi: 10.1016/j.neuron.2008.02.003
- Cohen, S. I., Linse, S., Luheshi, L. M., Hellstrand, E., White, D. A., Rajah, L., et al. (2013). Proliferation of amyloid-beta42 aggregates occurs through a secondary nucleation mechanism. *Proc. Natl. Acad. Sci. U. S. A.* 110, 9758–9763. doi: 10.1073/pnas.1218402110
- Cohen, T. J., Guo, J. L., Hurtado, D. E., Kwong, L. K., IMills, L. P., Trojanowski, J. Q., et al. (2011). The acetylation of tau inhibits its function and promotes pathological tau aggregation. *Nat. Commun.* 2:252. doi: 10.1038/ncomms1255

- Colvin, M. T., Silvers, R., Ni, Q. Z., Can, T. V., Sergeev, L., Rosay, M., et al. (2016). Atomic Resolution Structure of Monomorphic Abeta42 Amyloid Fibrils. *J. Am. Chem. Soc.* 138, 9663–9674. doi: 10.1021/jacs.6b05129
- Correia, S. C., Resende, R., Moreira, P. I., and Pereira, C. M. (2015). Alzheimer's disease-related misfolded proteins and dysfunctional organelles on autophagy menu. *DNA Cell Biol.* 34, 261–273. doi: 10.1089/dna.2014.2757
- Crane, A., Brubaker, W. D., Johansson, J. U., Trigunait, A., Ceballos, J., Bradt, B., et al. (2018). Peripheral complement interactions with amyloid beta peptide in Alzheimer's disease: 2. Relationship to amyloid beta immunotherapy. *Alzheimers Dement* 14, 243–252. doi: 10.1016/j.jalz.2017.04.015
- Cui, S., Xiong, F., Hong, Y., Jung, J. U., Li, X. S., Liu, J. Z., et al. (2011). APPswe/Abeta regulation of osteoclast activation and RAGE expression in an age-dependent manner. *J. Bone Miner Res.* 26, 1084–1098. doi: 10.1002/jbmr.299
- Cummings, J. L., Cohen, S., van Dyck, C. H., Brody, M., Curtis, C., Cho, W., et al. (2018). ABBY: A phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease. *Neurology* 90, e1889–e1897. doi: 10.1212/wnl.0000000000005550
- Das, U., Scott, D. A., Ganguly, A., Koo, E. H., Tang, Y., and Roy, S. (2013). Activity-induced convergence of APP and BACE-1 in acidic microdomains via an endocytosis-dependent pathway. *Neuron* 79, 447–460. doi: 10.1016/j.neuron.2013.05.035
- De Felice, F. G., Vieira, M. N., Bomfim, T. R., Decker, H., Velasco, P. T., Lambert, M. P., et al. (2009). Protection of synapses against Alzheimer's-linked toxins: Insulin signaling prevents the pathogenic binding of Abeta oligomers. *Proc. Natl. Acad. Sci. U. S. A.* 106, 1971–1976. doi: 10.1073/pnas.0809158106
- de Jager, M., Boot, M. V., Bol, J. G., Brevé, J. J., Jongenelen, C. A., Drukarch, B., et al. (2016). The blood clotting Factor XIIIa forms unique complexes with amyloid-beta (Abeta) and colocalizes with deposited Abeta in cerebral amyloid angiopathy. *Neuropathol. Appl. Neurobiol.* 42, 255–272. doi: 10.1111/nan.12244
- De Strooper, B., and Chavez Gutierrez, L. (2015). Learning by failing: Ideas and concepts to tackle gamma-secretases in Alzheimer's disease and beyond. *Annu. Rev. Pharmacol. Toxicol.* 55, 419–437. doi: 10.1146/annurev-pharmtox-010814-124309
- De Strooper, B., Vassar, R., and Golde, T. (2010). The secretases: Enzymes with therapeutic potential in Alzheimer disease. *Nat. Rev. Neurol.* 6, 99–107. doi: 10.1038/nrneuro.2009.218
- Del Turco, D., Paul, M. H., Schlaudraff, J., Hick, M., Endres, K., Müller, U. C., et al. (2016). Region-Specific Differences in Amyloid Precursor Protein Expression in the Mouse Hippocampus. *Front. Mol. Neurosci.* 9:134. doi: 10.3389/fnmol.2016.00134
- Dilna, A., Deepak, K. V., Damodaran, N., Kielkopf, C. S., Kagedal, K., Ollinger, K., et al. (2021). Amyloid- $\beta$  induced membrane damage instigates tunneling nanotube-like conduits by p21-activated kinase dependent actin remodeling. *Biochim. Biophys. Acta Mol. Basis Dis.* 1867:166246. doi: 10.1016/j.bbadis.2021.166246
- Domert, J., Rao, S. B., Agholme, L., Brorsson, A. C., Marcusson, J., Hallbeck, M., et al. (2014). Spreading of amyloid-beta peptides via neuritic cell-to-cell transfer is dependent on insufficient cellular clearance. *Neurobiol. Dis.* 65, 82–92. doi: 10.1016/j.nbd.2013.12.019
- Economou, N. J., Giammona, M. J., Do, T. D., Zheng, X. Y., Teplow, D. B., Buratto, S. K., et al. (2016). Amyloid beta-Protein Assembly and Alzheimer's Disease: Dodecamers of Abeta42, but Not of Abeta40, Seed Fibril Formation. *J. Am. Chem. Soc.* 138, 1772–1775. doi: 10.1021/jacs.5b11913
- Egan, M. F., Kost, J., Tariot, P. N., Aisen, P. S., Cummings, J. L., Vellas, B., et al. (2018). Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease. *N. Engl. J. Med.* 378, 1691–1703. doi: 10.1056/NEJMoa1706441
- Egan, M. F., Kost, J., Voss, T., Mukai, Y., Aisen, P. S., Cummings, J. L., et al. (2019). Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease. *N. Engl. J. Med.* 380, 1408–1420. doi: 10.1056/NEJMoa1812840
- Eisenberg, D. S., and Sawaya, M. R. (2016). Implications for Alzheimer's disease of an atomic resolution structure of amyloid-beta(1-42) fibrils. *Proc. Natl. Acad. Sci. U. S. A.* 113, 9398–9400. doi: 10.1073/pnas.1610806113
- Erickson, M. A., Hansen, K., and Banks, W. A. (2012). Inflammation-induced dysfunction of the low-density lipoprotein receptor-related protein-1 at the blood-brain barrier: Protection by the antioxidant N-acetylcysteine. *Brain Behav. Immun.* 26, 1085–1094. doi: 10.1016/j.bbi.2012.07.003
- Esparza, T. J., Wildburger, N. C., Jiang, H., Gangolli, M., Cairns, N. J., Bateman, R. J., et al. (2016). Soluble Amyloid-beta Aggregates from Human Alzheimer's Disease Brains. *Sci. Rep.* 6:38187. doi: 10.1038/srep38187
- Fang, E. F., Hou, Y. J., Palikaras, K., Adriaanse, B. A., Kerr, J. S., Yang, B., et al. (2019). Mitophagy inhibits amyloid-beta and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat. Neurosci.* 22, 401–412. doi: 10.1038/s41593-018-0332-9
- Fawer, J. N., Ghiwot, Y., Koola, C., Carrera, W., Rodriguez-Rivera, J., Hernandez, C., et al. (2014). Islet amyloid polypeptide (IAPP): A second amyloid in Alzheimer's disease. *Curr. Alzheimer Res.* 11, 928–940. doi: 10.2174/1567205011666141107124538
- Fitzpatrick, A. W. P., Falcon, B., He, S., Murzin, A. G., Murshudov, G., Garringer, H. J., et al. (2017). Cryo-EM structures of tau filaments from Alzheimer's disease. *Nature* 547, 185–190. doi: 10.1038/nature23002
- Fuller, J. P., Stavenhagen, J. B., Christensen, S., Kartberg, F., Glennie, M., and Teeling, J. L. (2015). Comparing the efficacy and neuroinflammatory potential of three anti-abeta antibodies. *Acta Neuropathol.* 130, 699–711. doi: 10.1007/s00401-015-1484-2
- Ghiso, J., Calero, M., Matsubara, E., Governale, S., Chuba, J., Beavis, R., et al. (1997). Alzheimer's soluble amyloid beta is a normal component of human urine. *FEBS Lett.* 408, 105–108. doi: 10.1016/s0014-5793(97)00400-6
- Ghiso, J., Shayo, M., Calero, M., Ng, D., Tomidokoro, Y., Gandy, S., et al. (2004). Systemic catabolism of Alzheimer's Abeta40 and Abeta42. *J. Biol. Chem.* 279, 45897–45908. doi: 10.1074/jbc.M407668200
- Gonzalez-Marrero, I., Giménez-Llort, L., Johanson, C. E., Carmona-Calero, E. M., Castañeyra-Ruiz, L., Brito-Armas, J. M., et al. (2015). Choroid plexus dysfunction impairs beta-amyloid clearance in a triple transgenic mouse model of Alzheimer's disease. *Front. Cell Neurosci.* 9:17. doi: 10.3389/fncel.2015.00017
- Gowrishankar, S., Yuan, P., Wu, Y., Schrag, M., Paradise, S., Grutzendler, J., et al. (2017). Massive accumulation of luminal protease-deficient axonal lysosomes at Alzheimer's disease amyloid plaques. *Proc. Natl. Acad. Sci. U. S. A.* 112, E3699–E3708. doi: 10.1073/pnas.1510329112
- Gremer, L., Schölzel, D., Schenk, C., Reinartz, E., Labahn, J., Ravelli, R. B., et al. (2017). Fibril structure of amyloid-beta(1-42) by cryo-electron microscopy. *Science* 358, 116–119. doi: 10.1126/science.aao2825
- Gronewold, J., Klafki, H. W., Baldelli, E., Kaltwasser, B., Seidel, U. K., Todica, O., et al. (2016). Factors Responsible for Plasma beta-Amyloid Accumulation in Chronic Kidney Disease. *Mol. Neurobiol.* 53, 3136–3145. doi: 10.1007/s12035-015-9218-y
- Gronewold, J., Todica, O., Klafki, H. W., Seidel, U. K., Kaltwasser, B., Wiltfang, J., et al. (2017). Association of Plasma beta-Amyloid with Cognitive Performance and Decline in Chronic Kidney Disease. *Mol. Neurobiol.* 54, 7194–7203. doi: 10.1007/s12035-016-0243-2
- Guenette, S. Y. (2003). Astrocytes: A cellular player in Abeta clearance and degradation. *Trends Mol. Med.* 9, 279–280. doi: 10.1016/s1471-4914(03)00112-6
- Haass, C., and Selkoe, D. J. (2007). Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid beta-peptide. *Nat. Rev. Mol. Cell Biol.* 8, 101–112. doi: 10.1038/nrm2101
- Hampel, H., Hardy, J., Blennow, K., Chen, C., Perry, G., Kim, S. H., et al. (2021). The Amyloid- $\beta$  Pathway in Alzheimer's Disease. *Mol. Psychiatr.* 26, 5481–5503. doi: 10.1038/s41380-021-01249-0
- Hansson, O., Stomrud, E., Vanmechelen, E., Östling, S., Gustafson, D. R., Zetterberg, H., et al. (2012). Evaluation of plasma Abeta as predictor of Alzheimer's disease in older individuals without dementia: A population-based study. *J. Alzheimers Dis.* 28, 231–238. doi: 10.3233/jad-2011-111418
- Hansson Petersen, C. A., Alikhani, N., Behbahani, H., Wiehager, B., Pavlov, P. F., Alafuzoff, I., et al. (2008). The amyloid beta-peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae. *Proc. Natl. Acad. Sci. U. S. A.* 105, 13145–13150. doi: 10.1073/pnas.0806192105
- Hardy, J. A., and Higgins, G. A. (1992). Alzheimer's disease: The amyloid cascade hypothesis. *Science* 256, 184–185. doi: 10.1126/science.1566067
- Harrison, R. S., Sharpe, P. C., Singh, Y., and Fairlie, D. P. (2007). Amyloid peptides and proteins in review. *Rev. Physiol. Biochem. Pharmacol.* 159, 1–77. doi: 10.1007/112\_2007\_0701
- Hatch, R. J., Wei, Y., Xia, D., and Gotz, J. (2017). Hyperphosphorylated tau causes reduced hippocampal CA1 excitability by relocating the axon initial segment. *Acta Neuropathol.* 133, 717–730. doi: 10.1007/s00401-017-1674-1
- Henley, D., Raghavan, N., Sperling, R., Aisen, P., Raman, R., and Romano, G. (2019). Preliminary Results of a Trial of Atabecestat in Preclinical Alzheimer's Disease. *N. Engl. J. Med.* 380, 1483–1485. doi: 10.1056/NEJMc1813435
- Herrup, K. (2015). The case for rejecting the amyloid cascade hypothesis. *Nat. Neurosci.* 18, 794–799. doi: 10.1038/nn.4017
- Hickman, S. E., Allison, E. K., and El Khoury, J. (2008). Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J. Neurosci.* 28, 8354–8360. doi: 10.1523/jneurosci.0616-08.2008
- Hong, S., Ostaszewski, B. L., Yang, T., O'Malley, T. T., Jin, M., Yanagisawa, K., et al. (2014). Soluble Abeta oligomers are rapidly sequestered from brain ISF



- in vivo and bind GM1 ganglioside on cellular membranes. *Neuron* 82, 308–319. doi: 10.1016/j.neuron.2014.02.027
- Honig, L. S., Vellas, B., Woodward, M., Boada, M., Bullock, R., Borrie, M., et al. (2018). Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease. *N. Engl. J. Med.* 378, 321–330. doi: 10.1056/NEJMoa1705971
- Hsia, A. Y., Masliah, E., McConlogue, L., Yu, G. Q., Tatsuno, G., Hu, K., et al. (1999). Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. *Proc. Natl. Acad. Sci. U. S. A.* 96, 3228–3233. doi: 10.1073/pnas.96.6.3228
- Hsu, J. L., Lee, W. J., Liao, Y. C., Wang, S. J., and Fuh, J. L. (2017). The clinical significance of plasma clusterin and Abeta in the longitudinal follow-up of patients with Alzheimer's disease. *Alzheimers Res. Ther.* 9:91. doi: 10.1186/s13195-017-0319-x
- Hughes, M. M., and O'Neill, L. A. J. (2018). Metabolic regulation of NLRP3. *Immunol. Rev.* 281, 88–98. doi: 10.1111/imr.12608
- Hulse, J., and Bhaskar, K. (2022). Crosstalk Between the NLRP3 Inflammasome/ASC Speck and Amyloid Protein Aggregates Drives Disease Progression in Alzheimer's and Parkinson's Disease. *Front. Mol. Neurosci.* 15:805169. doi: 10.3389/fnmol.2022.805169
- Illiff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., et al. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci. Transl. Med.* 4:147ra111. doi: 10.1126/scitranslmed.3003748
- Irwin, D. J., Cohen, T. J., Grossman, M., Arnold, S. E., Xie, S. X., Lee, V. M. Y., et al. (2012). Acetylated tau, a novel pathological signature in Alzheimer's disease and other tauopathies. *Brain* 135, 807–818. doi: 10.1093/brain/awo013
- Iscen, A., Brue, C. R., Roberts, K. F., Kim, J., Schatz, G. C., Meade, T. J., et al. (2019). Inhibition of Amyloid-beta Aggregation by Cobalt(III) Schiff Base Complexes: A Computational and Experimental Approach. *J. Am. Chem. Soc.* 141, 16685–16695. doi: 10.1021/jacs.9b06388
- Ising, C., Venegas, C., Zhang, S., Scheiblich, H., Schmidt, S. V., Vieira-Saecker, A., et al. (2019). NLRP3 inflammasome activation drives tau pathology. *Nature* 575, 669–673. doi: 10.1038/s41586-019-1769-z
- Ittner, L. M., Ke, Y. D., Delerue, F., Bi, M., Gladbach, A., van Eersel, J., et al. (2010). Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. *Cell* 142, 387–397. doi: 10.1016/j.cell.2010.06.036
- Jackson, K., Barisone, G. A., Diaz, E., Jin, L., DeCarli, C., and Despa, F. (2013). Amylin deposition in the brain: A second amyloid in Alzheimer disease? *Ann. Neurol.* 74, 517–526. doi: 10.1002/ana.23956
- Jackson, S. J., Kerridge, C., Cooper, J., Cavallini, A., Falcon, B., Cella, C. V., et al. (2016). Short Fibrils Constitute the Major Species of Seed-Competent Tau in the Brains of Mice Transgenic for Human P301S Tau. *J. Neurosci.* 36, 762–772. doi: 10.1523/jneurosci.3542-15.2016
- Janczura, K. J., Volmar, C. H., Sartor, G. C., Rao, S. J., Ricciardi, N. R., Lambert, G., et al. (2018). Inhibition of HDAC3 reverses Alzheimer's disease-related pathologies in vitro and in the 3xTg-AD mouse model. *Proc. Natl. Acad. Sci. U. S. A.* 115, E11148–E11157. doi: 10.1073/pnas.1805436115
- Janson, J., Ashley, R. H., Harrison, D., McIntyre, S., and Butler, P. C. (1999). The mechanism of islet amyloid polypeptide toxicity is membrane disruption by intermediate-sized toxic amyloid particles. *Diabetes* 48, 491–498. doi: 10.2337/diabetes.48.3.491
- Jaunmuktane, Z., Mead, S., Ellis, M., Wadsworth, J. D., Nicoll, A. J., Kenny, J., et al. (2015). Evidence for human transmission of amyloid-beta pathology and cerebral amyloid angiopathy. *Nature* 525, 247–250. doi: 10.1038/nature15369
- Jaya Prasanthi, R. P., Schommer, E., Thomasson, S., Thompson, A., Feist, G., and Ghribi, O. (2008). Regulation of beta-amyloid levels in the brain of cholesterol-fed rabbit, a model system for sporadic Alzheimer's disease. *Mech. Ageing Dev.* 129, 649–655. doi: 10.1016/j.mad.2008.09.002
- Jiao, S. S., Yao, X. Q., Liu, Y. H., Wang, Q. H., Zeng, F., Lu, J. J., et al. (2015). Edaravone alleviates Alzheimer's disease-type pathologies and cognitive deficits. *Proc. Natl. Acad. Sci. U. S. A.* 112, 5225–5230. doi: 10.1073/pnas.1422998112
- Jin, W. S., Shen, L. L., Bu, X. L., Zhang, W. W., Chen, S. H., Huang, Z. L., et al. (2017). Peritoneal dialysis reduces amyloid-beta plasma levels in humans and attenuates Alzheimer-associated phenotypes in an APP/PS1 mouse model. *Acta Neuro.* 134, 207–220. doi: 10.1007/s00401-017-1721-y
- Johanson, C. E., Johanson, C. E., Duncan, J. A. III, Klinge, P. M., Brinker, T., Stopa, E. G., et al. (2008). Multiplicity of cerebrospinal fluid functions: New challenges in health and disease. *Cerebrospinal. Fluid Res.* 5:10. doi: 10.1186/1743-8454-5-10
- Jung, E. S., Hong, H., Kim, C., and Mook-Jung, I. (2015). Acute ER stress regulates amyloid precursor protein processing through ubiquitin-dependent degradation. *Sci. Rep.* 5:8805. doi: 10.1038/srep08805
- Kadavath, H., Jaremko, M., Jaremko, L., Biernat, J., Mandelkow, E., and Zweckstetter, M. (2015). Folding of the Tau Protein on Microtubules. *Angew. Chem. Int. Ed Engl.* 54, 10347–10351. doi: 10.1002/anie.201501714
- Kanemitsu, H., Tomiyama, T., and Mori, H. (2003). Human neprilysin is capable of degrading amyloid beta peptide not only in the monomeric form but also the pathological oligomeric form. *Neurosci. Lett.* 350, 113–116. doi: 10.1016/s0304-3940(03)00898-x
- Kawarabayashi, T., Shoji, M., Younkin, L. H., Wen-Lang, L., Dickson, D. W., Murakami, T., et al. (2004). Dimeric amyloid beta protein rapidly accumulates in lipid rafts followed by apolipoprotein E and phosphorylated tau accumulation in the Tg2576 mouse model of Alzheimer's disease. *J. Neurosci.* 24, 3801–3809. doi: 10.1523/jneurosci.5543-03.2004
- Kim, D., Kwon, H. J., and Hyeon, T. (2019). Magnetite/Ceria Nanoparticle Assemblies for Extracorporeal Cleansing of Amyloid-beta in Alzheimer's Disease. *Adv. Mater.* 31:e1807965. doi: 10.1002/adma.201807965
- Kim, D. I., Lee, K. H., Oh, J. Y., Kim, J. S., and Han, H. J. (2017). Relationship Between beta-Amyloid and Mitochondrial Dynamics. *Cell Mol. Neurobiol.* 37, 955–968. doi: 10.1007/s10571-016-0434-4
- Kim, T., Vidal, G. S., Djurisic, M., William, C. M., Birnbaum, M. E., Garcia, K. C., et al. (2013). Human LILRB2 is a beta-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. *Science* 341, 1399–1404. doi: 10.1126/science.1242077
- Klein, C., Roussel, G., Brun, S., Rusu, C., Patte-Mensah, C., Maitre, M., et al. (2018). 5-HIAA induces neprilysin to ameliorate pathophysiology and symptoms in a mouse model for Alzheimer's disease. *Acta Neuro.* 6:136. doi: 10.1186/s40478-018-0640-z
- Knight, S. D., Presto, J., Linse, S., and Johansson, J. (2013). The BRICHOS domain, amyloid fibril formation, and their relationship. *Biochemistry* 52, 7523–7531. doi: 10.1021/bi400908x
- Kopeikina, K. J., Carlson, G. A., Pitstick, R., Ludvigson, A. E., Peters, A., Luebke, J. I., et al. (2011). Tau accumulation causes mitochondrial distribution deficits in neurons in a mouse model of tauopathy and in human Alzheimer's disease brain. *Am. J. Pathol.* 179, 2071–2082. doi: 10.1016/j.ajpath.2011.07.004
- Kress, B. T., Illiff, J. J., Xia, M., Wang, M., Wei, H. S., Zeppenfeld, D., et al. (2014). Impairment of paravascular clearance pathways in the aging brain. *Ann. Neurol.* 76, 845–861. doi: 10.1002/ana.24271
- Kuo, Y. M., Emmerling, M. R., Lampert, H. C., Hempelman, S. R., Kokjohn, T. A., Woods, A. S., et al. (1999). High levels of circulating Abeta42 are sequestered by plasma proteins in Alzheimer's disease. *Biochem. Biophys. Res. Commun.* 257, 787–791. doi: 10.1006/bbrc.1999.0552
- Kuo, Y. M., Kokjohn, T. A., Kalback, W., Luehrs, D., Galasko, D. R., Chevallier, N., et al. (2000a). Amyloid-beta peptides interact with plasma proteins and erythrocytes: Implications for their quantitation in plasma. *Biochem. Biophys. Res. Commun.* 268, 750–756. doi: 10.1006/bbrc.2000.2222
- Kuo, Y. M., Kokjohn, T. A., Watson, M. D., Woods, A. S., Cotter, R. J., Sue, L. I., et al. (2000b). Elevated abeta42 in skeletal muscle of Alzheimer disease patients suggests peripheral alterations of AbetaPP metabolism. *Am. J. Pathol.* 156, 797–805. doi: 10.1016/s0002-9440(10)64947-4
- Ladiwala, A. R., Dordick, J. S., and Tessier, P. M. (2011). Aromatic small molecules remodel toxic soluble oligomers of amyloid beta through three independent pathways. *J. Biol. Chem.* 286, 3209–3218. doi: 10.1074/jbc.M110.173856
- Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., et al. (1998). Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. *Proc. Natl. Acad. Sci. U. S. A.* 95, 6448–6453. doi: 10.1073/pnas.95.11.6448
- Lau, T. L., Gehman, J. D., Wade, J. D., Perez, K., Masters, C. L., Barnham, K. J., et al. (2007). Membrane interactions and the effect of metal ions of the amyloidogenic fragment Abeta(25-35) in comparison to Abeta(1-42). *Biochim. Biophys. Acta* 1768, 2400–2408. doi: 10.1016/j.bbame.2007.05.004
- Law, B. M., Guest, A. L., Pullen, M. W. J., Perkinson, M. S., and Williams, R. J. (2018). Increased Foxo3a Nuclear Translocation and Activity is an Early Neuronal Response to betagamma-Secretase-Mediated Processing of the Amyloid-beta Protein Precursor: Utility of an AbetaPP-GAL4 Reporter Assay. *J. Alzheimers Dis.* 61, 673–688. doi: 10.3233/jad-170393
- Lee, C. Y., and Landreth, G. E. (2010). The role of microglia in amyloid clearance from the AD brain. *J. Neural. Transm.* 117, 949–960. doi: 10.1007/s00702-010-0433-4
- Lesne, S., Koh, M. T., Kotilinek, L., Kaye, R., Glabe, C. G., Yang, A., et al. (2006). A specific amyloid-beta protein assembly in the brain impairs memory. *Nature* 440, 352–357. doi: 10.1038/nature04533



- Li, C., and Gotz, J. (2017). Somatodendritic accumulation of Tau in Alzheimer's disease is promoted by Fyn-mediated local protein translation. *EMBO J.* 36, 3120–3138. doi: 10.15252/embj.201797724
- Li, J., Wang, Y. J., Zhang, M., Xu, Z. Q., Gao, C. Y., Fang, C. Q., et al. (2011). Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology* 76, 1485–1491. doi: 10.1212/WNL.0b013e318217e7a4
- Li, S., Liu, B., Zhang, L., and Rong, L. (2014). Amyloid beta peptide is elevated in osteoporotic bone tissues and enhances osteoclast function. *Bone* 61, 164–175. doi: 10.1016/j.bone.2014.01.010
- Li, X., Uemura, K., Hashimoto, T., Nasser-Ghods, N., Arimon, M., Lill, C. M., et al. (2013). Neuronal activity and secreted amyloid beta lead to altered amyloid beta precursor protein and presenilin 1 interactions. *Neurobiol. Dis.* 50, 127–134. doi: 10.1016/j.nbd.2012.10.002
- Lim, N. K., Villemagne, V. L., Soon, C. P., Laughton, K. M., Rowe, C. C., McLean, C. A., et al. (2011). Investigation of matrix metalloproteinases, MMP-2 and MMP-9, in plasma reveals a decrease of MMP-2 in Alzheimer's disease. *J. Alzheimers Dis.* 26, 779–786. doi: 10.3233/jad-2011-101974
- Ling, X., Martins, R. N., Racchi, M., Craft, S., and Helmerhorst, E. (2002). Amyloid beta antagonizes insulin promoted secretion of the amyloid beta protein precursor. *J. Alzheimers Dis.* 4, 369–374. doi: 10.3233/jad-2002-4504
- Liu, Y. H., Xiang, Y., Wang, Y. R., Jiao, S. S., Wang, Q. H., Bu, X. L., et al. (2015). Association Between Serum Amyloid-Beta and Renal Functions: Implications for Roles of Kidney in Amyloid-Beta Clearance. *Mol. Neurobiol.* 52, 115–119. doi: 10.1007/s12035-014-8854-y
- Lovheim, H., Elgh, F., Johansson, A., Zetterberg, H., Blennow, K., Hallmans, G., et al. (2017). Plasma concentrations of free amyloid beta cannot predict the development of Alzheimer's disease. *Alzheimers Dement* 13, 778–782. doi: 10.1016/j.jalz.2016.12.004
- Lu, J. X., Qiang, W., Yau, W. M., Schwieters, C. D., Meredith, S. C., and Tycko, R. (2013). Molecular structure of beta-amyloid fibrils in Alzheimer's disease brain tissue. *Cell* 154, 1257–1268. doi: 10.1016/j.cell.2013.08.035
- Lucin, K. M., and Wyss-Coray, T. (2009). Immune activation in brain aging and neurodegeneration: Too much or too little? *Neuron* 64, 110–122. doi: 10.1016/j.neuron.2009.08.039
- Mairet-Coello, G., Courchet, J., Pieraut, S., Courchet, V., Maximov, A., and Polleux, F. (2013). The CAMKK2-AMPK kinase pathway mediates the synaptotoxic effects of Abeta oligomers through Tau phosphorylation. *Neuron* 78, 94–108. doi: 10.1016/j.neuron.2013.02.003
- Maler, J. M., Spitzer, P., Klafki, H. W., Esselmann, H., Lewczuk, P., Kornhuber, J., et al. (2009). Distinct fractional Abeta release patterns in human mononuclear phagocytes. *J. Neuroimmunol.* 206, 1–4. doi: 10.1016/j.jneuroim.2008.08.010
- Mawuenyega, K. G., Sigurdson, W., Ovod, V., Munsell, L., Kasten, T., Morris, J. C., et al. (2010). Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science* 330:1774. doi: 10.1126/science.1197623
- McGowan, E., Pickford, F., Kim, J., Onstead, L., Eriksen, J., Yu, C., et al. (2005). Abeta42 is essential for parenchymal and vascular amyloid deposition in mice. *Neuron* 47, 191–199. doi: 10.1016/j.neuron.2005.06.030
- Menendez-Gonzalez, M., and Gasparovic, C. (2019). Albumin Exchange in Alzheimer's Disease: Might CSF Be an Alternative Route to Plasma? *Front. Neurol.* 10:1036. doi: 10.3389/fneur.2019.01036
- Michno, W., Blennow, K., Zetterberg, H., and Brinkmalm, G. (2021). Refining the amyloid  $\beta$  peptide and oligomer fingerprint ambiguities in Alzheimer's disease: Mass spectrometric molecular characterization in brain, cerebrospinal fluid, blood, and plasma. *J. Neurochem.* 159, 234–257. doi: 10.1111/jnc.15466
- Miller, Y., Ma, B., Tsai, C. J., and Nussinov, R. (2010). Hollow core of Alzheimer's Abeta42 amyloid observed by cryoEM is relevant at physiological pH. *Proc. Natl. Acad. Sci. U. S. A.* 107, 14128–14133. doi: 10.1073/pnas.1004704107
- Min, S. W., Chen, X., Tracy, T. E., Li, Y., Zhou, Y., Wang, C., et al. (2015). Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. *Nat. Med.* 21, 1154–1162. doi: 10.1038/nm.3951
- Min, S. W., Cho, S. H., Zhou, Y., Schroeder, S., Haroutunian, V., Seeley, W. W., et al. (2010). Acetylation of tau inhibits its degradation and contributes to tauopathy. *Neuron* 67, 953–966. doi: 10.1016/j.neuron.2010.08.044
- Montane, J., Klimek-Abercrombie, A., Potter, K. J., Westwell-Roper, C., and Bruce Vercher, C. (2012). Metabolic stress, IAPP and islet amyloid. *Diabetes. Obes. Metab.* 3, 68–77. doi: 10.1111/j.1463-1326.2012.01657.x
- Moreno-Gonzalez, I., Iii, G. E., Salvadores, N., Shah Nawaz, M., Diaz-Espinoza, R., and Soto, C. (2017). Molecular interaction between type 2 diabetes and Alzheimer's disease through cross-seeding of protein misfolding. *Mol. Psychiat.* 22, 1327–1334. doi: 10.1038/mp.2016.230
- Morrone, C. D., Liu, M., Black, S. E., and McLaurin, J. (2015). Interaction between therapeutic interventions for Alzheimer's disease and physiological Abeta clearance mechanisms. *Front. Aging Neurosci.* 7:64. doi: 10.3389/fnagi.2015.00064
- Nabers, A., Ollesch, J., Schartner, J., Kötting, C., Genius, J., Hafermann, H., et al. (2016). Amyloid-beta-Secondary Structure Distribution in Cerebrospinal Fluid and Blood Measured by an Immuno-Infrared-Sensor: A Biomarker Candidate for Alzheimer's Disease. *Ana. Chem.* 88, 2755–2762. doi: 10.1021/acs.analchem.5b04286
- Nabers, A., Perna, L., Lange, J., Mons, U., Schartner, J., Guldnhaupt, J., et al. (2018). Amyloid blood biomarker detects Alzheimer's disease. *EMBO Mol. Med.* 10:e8763. doi: 10.15252/emmm.201708763
- Nagele, R. G., D'Andrea, M. R., Lee, H., Venkataraman, V., and Wang, H. Y. (2003). Astrocytes accumulate A beta 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. *Brain Res.* 971, 197–209. doi: 10.1016/s0006-8993(03)02361-8
- Nakamura, A., Kaneko, N., Villemagne, V. L., Kato, T., Doecke, J., Doré, V., et al. (2018). High performance plasma amyloid-beta biomarkers for Alzheimer's disease. *Nature* 554, 249–254. doi: 10.1038/nature25456
- Nguyen, P., and Derreumaux, P. (2014). Understanding amyloid fibril nucleation and abeta oligomer/drug interactions from computer simulations. *Acc. Chem. Res.* 47, 603–611. doi: 10.1021/ar4002075
- Niederst, E. D., Reyna, S. M., and Goldstein, L. S. (2015). Axonal amyloid precursor protein and its fragments undergo somatodendritic endocytosis and processing. *Mol. Biol. Cell.* 26, 205–217. doi: 10.1091/mbc.E14-06-1049
- Nixon, R. A. (2007). Autophagy, amyloidogenesis and Alzheimer disease. *J. Cell Sci.* 120, 4081–4091. doi: 10.1242/jcs.019265
- Nixon, R. A., and Cataldo, A. M. (2006). Lysosomal system pathways: Genes to neurodegeneration in Alzheimer's disease. *J. Alzheimers Dis.* 9, 277–289. doi: 10.3233/jad-2006-9s331
- Noguchi, A., Matsumura, S., Dezawa, M., Tada, M., Yanazawa, M., Ito, A., et al. (2009). Isolation and characterization of patient-derived, toxic, high mass amyloid beta-protein (Abeta) assembly from Alzheimer disease brains. *J. Biol. Chem.* 284, 32895–32905. doi: 10.1074/jbc.M109.000208
- Norambuena, A., Wallrabe, H., Cao, R., Wang, D. B., Silva, A., Svindrych, Z., et al. (2018). A novel lysosome-to-mitochondria signaling pathway disrupted by amyloid-beta oligomers. *EMBO J.* 37:e100241. doi: 10.15252/embj.2018100241
- Ono, K., Li, L., Takamura, Y., Yoshiike, Y., Zhu, L., Han, F., et al. (2012). Phenolic compounds prevent amyloid beta-protein oligomerization and synaptic dysfunction by site-specific binding. *J. Biol. Chem.* 287, 14631–14643. doi: 10.1074/jbc.M111.325456
- Pan, R. Y., Ma, J., Kong, X. X., Wang, X. F., Li, S. S., Qi, X. L., et al. (2019). Sodium rutin ameliorates Alzheimer's disease-like pathology by enhancing microglial amyloid-beta clearance. *Sci. Adv.* 5:eau6328. doi: 10.1126/sciadv.aau6328
- Pearson, H. A., and Peers, C. (2006). Physiological roles for amyloid beta peptides. *J. Physiol.* 575, 5–10. doi: 10.1113/jphysiol.2006.111203
- Perez, F. P., Bose, D., Maloney, B., Nho, K., Shah, K., and Lahiri, D. K. (2014). Late-onset Alzheimer's disease, heating up and foxed by several proteins: Pathomolecular effects of the aging process. *J. Alzheimers Dis.* 40, 1–17. doi: 10.3233/jad-131544
- Perry, V. H., Nicoll, J. A., and Holmes, C. (2010). Microglia in neurodegenerative disease. *Nat. Rev. Neurol.* 6, 193–201. doi: 10.1038/nrneuro.2010.17
- Petkova, A. T., Ishii, Y., Balbach, J. J., Antzutkin, O. N., Leapman, R. D., Delaglio, F., et al. (2002). A structural model for Alzheimer's beta-amyloid fibrils based on experimental constraints from solid state NMR. *Proc. Natl. Acad. Sci. U. S. A.* 99, 16742–16747. doi: 10.1073/pnas.262663499
- Polanco, J. C., Li, C., Bodea, L. G., Martinez-Marmol, R., Meunier, F. A., and Götz, J. (2018). Amyloid-beta and tau complexity - towards improved biomarkers and targeted therapies. *Nat. Rev. Neurol.* 14, 22–39. doi: 10.1038/nrneuro.2017.162
- Poon, W. W., Carlos, A. J., Aguilar, B. L., Berchtold, N. C., Kawano, C. K., Zograbyan, V., et al. (2013). Beta-Amyloid (Abeta) oligomers impair brain-derived neurotrophic factor retrograde trafficking by down-regulating ubiquitin C-terminal hydrolase. UCH-L1. *J. Biol. Chem.* 288, 16937–16948. doi: 10.1074/jbc.M113.463711
- Puzzo, D., Gulisano, W., Arancio, O., and Palmeri, A. (2015). The keystone of Alzheimer pathogenesis might be sought in Abeta physiology. *Neuroscience* 307, 26–36. doi: 10.1016/j.neuroscience.2015.08.039
- Puzzo, D., Piacentini, R., Fá, M., Gulisano, W., Li Puma, D. D., Staniszewski, A., et al. (2017). LTP and memory impairment caused by extracellular Abeta and Tau oligomers is APP-dependent. *Elife* 6:e26991. doi: 10.7554/eLife.26991

- Puzzo, D., Privitera, L., Leznik, E., Fà, M., Staniszewski, A., Palmeri, A., et al. (2008). Picomolar amyloid-beta positively modulates synaptic plasticity and memory in hippocampus. *J. Neurosci.* 28, 14537–14545. doi: 10.1523/jneurosci.2692-08.2008
- Querfurth, H. W., and LaFerla, F. M. (2010). Alzheimer's disease. *N. Engl. J. Med.* 362, 329–344. doi: 10.1056/NEJMra0909142
- Rajendran, L., Honsho, M., Zahn, T. R., Keller, P., Geiger, K. D., Verkade, P., et al. (2006). Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc. Natl. Acad. Sci. U.S.A.* 103, 11172–11177. doi: 10.1073/pnas.0603838103
- Resende, R., Ferreira, E., Pereira, C., Resende, and de Oliveira, C. (2008). Neurotoxic effect of oligomeric and fibrillar species of amyloid-beta peptide 1-42: Involvement of endoplasmic reticulum calcium release in oligomer-induced cell death. *Neuroscience* 155, 725–737. doi: 10.1016/j.neuroscience.2008.06.036
- Rhein, V., Song, X., Wiesner, A., Ittner, L. M., Baysang, G., Meier, F., et al. (2009). Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. *Proc. Natl. Acad. Sci. U. S. A.* 106, 20057–20062. doi: 10.1073/pnas.0905529106
- Riek, R., and Eisenberg, D. S. (2016). The activities of amyloids from a structural perspective. *Nature* 539, 227–235. doi: 10.1038/nature20416
- Rochet, J. C., and Lansbury, P. T. Jr. (2000). Amyloid fibrillogenesis: Themes and variations. *Curr. Opin. Struct. Biol.* 10, 60–68. doi: 10.1016/s0959-440x(99)00049-4
- Roher, A. E., Esh, C. L., Kokjohn, T. A., Castaño, E. M., Van Vickle, G. D., Kalback, W. M., et al. (2009). Amyloid beta peptides in human plasma and tissues and their significance for Alzheimer's disease. *Alzheimers Dement* 5, 18–29. doi: 10.1016/j.jalz.2008.10.004
- Rustum, A., Saffrich, R., Markovic, I., Walther, P., and Gerdes, H. H. (2004). Nanotubular highways for intercellular organelle transport. *Science* 303, 1007–1010. doi: 10.1126/science.1093133
- Sagare, A. P., Deane, R., and Zlokovic, B. V. (2012). Low-density lipoprotein receptor-related protein 1: A physiological Abeta homeostatic mechanism with multiple therapeutic opportunities. *Pharmacol. Ther.* 136, 94–105. doi: 10.1016/j.pharmthera.2012.07.008
- Sambamurti, K., Greig, N. H., Utsuki, T., Barnwell, E. L., Sharma, E., Mazell, C., et al. (2011). Targets for AD treatment: Conflicting messages from gamma-secretase inhibitors. *J. Neurochem.* 117, 359–374. doi: 10.1111/j.1471-4159.2011.07213.x
- Sarroukh, R., Cerf, E., Derclaye, S., Dufrene, Y. F., Goormaghtigh, E., Ruysschaert, J. M., et al. (2011). Transformation of amyloid beta(1-40) oligomers into fibrils is characterized by a major change in secondary structure. *Cell Mol. Life Sci.* 68, 1429–1438. doi: 10.1007/s00018-010-0529-x
- Scheidt, T., Łapińska, U., Kumita, J. R., Whiten, D. R., Klenerman, D., Wilson, M. R., et al. (2019). Secondary nucleation and elongation occur at different sites on Alzheimer's amyloid-beta aggregates. *Sci. Adv.* 5:eau3112. doi: 10.1126/sciadv.aau3112
- Schelle, J., Wegenast-Braun, B. M., Fritsch, S. K., Kaeser, S. A., Jähring, N., Eicke, D., et al. (2019). Early Abeta reduction prevents progression of cerebral amyloid angiopathy. *Ann. Neurol.* 86, 561–571. doi: 10.1002/ana.25562
- Schmidt, M., Rohou, A., Lasker, K., Yadav, J. K., Schiene-Fischer, C., Fändrich, M., et al. (2015). Peptide dimer structure in an Abeta(1-42) fibril visualized with cryo-EM. *Proc. Natl. Acad. Sci. U. S. A.* 112, 11858–11863. doi: 10.1073/pnas.1503455112
- Schreiner, B., Hedskog, L., Wiehager, B., and Ankarcrona, M. (2015). Amyloid-β peptides are generated in mitochondria-associated endoplasmic reticulum membranes. *J. Alzheimers Dis.* 43, 369–374. doi: 10.3233/JAD-132543
- Schroeder, B. E., and Koo, E. H. (2005). To think or not to think: Synaptic activity and Abeta release. *Neuron* 48, 873–875. doi: 10.1016/j.neuron.2005.12.005
- Schutz, A. K., Vagt, T., Huber, M., Ovchinnikova, O. Y., Cadalbert, R., Wall, J., et al. (2015). Atomic-resolution three-dimensional structure of amyloid beta fibrils bearing the Osaka mutation. *Angew. Chem. Int. Ed. Engl.* 54, 331–335. doi: 10.1002/anie.201408598
- Sehgal, N., Gupta, A., Valli, R. K., Joshi, S. D., Mills, J. T., Hamel, E., et al. (2012). Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. *Proc. Natl. Acad. Sci. U. S. A.* 109, 3510–3515. doi: 10.1073/pnas.1112209109
- Selkoe, D. (2019). beta-secretase inhibitors for Alzheimer's disease: Heading in the wrong direction? *Lancet Neurol.* 18, 624–626. doi: 10.1016/s1474-4422(19)30202-9
- Serpell, L. C., Berriman, J., Jakes, R., Goedert, M., and Crowther, R. A. (2000). Fiber diffraction of synthetic alpha-synuclein filaments shows amyloid-like cross-beta conformation. *Proc. Natl. Acad. Sci. U. S. A.* 97, 4897–4902. doi: 10.1073/pnas.97.9.4897
- Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., et al. (2017). Addendum: The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. *Nature* 546:564. doi: 10.1038/nature22809
- Shankar, G. M., Li, S., Mehta, T. H., Garcia-Munoz, A., Shepardson, N. E., Smith, I., et al. (2008). Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* 14, 837–842. doi: 10.1038/nm1782
- Siegel, G., Gerber, H., Koch, P., Bruestle, O., Fraering, P. C., and Rajendran, L. (2017). The Alzheimer's Disease gamma-Secretase Generates Higher 42:40 Ratios for beta-Amyloid Than for p3 Peptides. *Cell Rep.* 19, 1967–1976. doi: 10.1016/j.celrep.2017.05.034
- Sinha, S., Lopes, D. H., Du, Z., Pang, E. S., Shanmugam, A., Lomakin, A., et al. (2011). Lysine-specific molecular tweezers are broad-spectrum inhibitors of assembly and toxicity of amyloid proteins. *J. Am. Chem. Soc.* 133, 16958–16969. doi: 10.1021/ja206279b
- Smith, D. G., Cappai, R., and Barnham, K. J. (2007). The redox chemistry of the Alzheimer's disease amyloid beta peptide. *Biochim. Biophys. Acta* 1768, 1976–1990. doi: 10.1016/j.bbame.2007.02.002
- Sonkar, V. K., Kulkarni, P. P., and Dash, D. (2014). Amyloid beta peptide stimulates platelet activation through RhoA-dependent modulation of actomyosin organization. *FASEB J.* 28, 1819–1829. doi: 10.1096/fj.13-243691
- Srodulski, S., Sharma, S., Bachstetter, A. B., Brelfoard, J. M., Pascual, C., Xie, X. S., et al. (2014). Neuroinflammation and neurologic deficits in diabetes linked to brain accumulation of amylin. *Mol. Neurodegener.* 9:30. doi: 10.1186/1750-1326-9-30
- Stanga, S., Vranx, C., Tasiaux, B., Marinangeli, C., Karlström, H., and Kienlen-Campard, P. (2018). Specificity of presenilin-1- and presenilin-2-dependent gamma-secretases towards substrate processing. *J. Cell. Mol. Med.* 22, 823–833. doi: 10.1111/jcmm.13364
- Stanyon, H. F., and Viles, J. H. (2012). Human serum albumin can regulate amyloid-beta peptide fiber growth in the brain interstitium: Implications for Alzheimer disease. *J. Biol. Chem.* 287, 28163–28168. doi: 10.1074/jbc.C112.360800
- Tagami, S., Yanagida, K., Kodama, T. S., Takami, M., Mizuta, N., Oyama, H., et al. (2017). Semagacestat Is a Pseudo-Inhibitor of gamma-Secretase. *Cell Rep.* 21, 259–273. doi: 10.1016/j.celrep.2017.09.032
- Takata, K., Kitamura, Y., Kakimura, J., Shibagaki, K., Tsuchiya, D., Taniguchi, T., et al. (2003). Role of high mobility group protein-1 (HMGI) in amyloid-beta homeostasis. *Biochem. Biophys. Res. Commun.* 301, 699–703. doi: 10.1016/s0006-291x(03)00024-x
- Talantova, M., Sanz-Blasco, S., Zhang, X., Xia, P., Akhtar, M. W., Okamoto, S., et al. (2013). Abeta induces astrocytic glutamate release, extrasynaptic NMDA receptor activation, and synaptic loss. *Proc. Natl. Acad. Sci. U. S. A.* 110, E2518–E2527. doi: 10.1073/pnas.1306832110
- Doody, R. S., Thomas, R. G., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S., et al. (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* 370, 311–321. doi: 10.1056/NEJMoa1312889
- Tian, D. Y., Cheng, Y., Zhuang, Z. Q., He, C. Y., Pan, Q. G., Tang, M. Z., et al. (2021). Physiological clearance of amyloid-beta by the kidney and its therapeutic potential for Alzheimer's disease. *Mol. Psychiat.* 26, 6074–6082. doi: 10.1038/s41380-021-01073-6
- Toledo, J. B., Vanderstichele, H., Figurski, M., Aisen, P. S., Petersen, R. C., Weiner, M. W., et al. (2011). Factors affecting Abeta plasma levels and their utility as biomarkers in ADNI. *Acta Neuropathol.* 122, 401–413. doi: 10.1007/s00401-011-0861-8
- Townsend, M., Shankar, G. M., Mehta, T., Walsh, D. M., and Selkoe, D. J. (2006). Effects of secreted oligomers of amyloid beta-protein on hippocampal synaptic plasticity: A potent role for trimers. *J. Physiol.* 572, 477–492. doi: 10.1113/jphysiol.2005.103754
- Tracy, T. E., Sohn, P. D., Minami, S. S., Wang, C., Min, S. W., Li, Y., et al. (2016). Acetylated Tau Obstructs KIBRA-Mediated Signaling in Synaptic Plasticity and Promotes Tauopathy-Related Memory Loss. *Neuron* 90, 245–260. doi: 10.1016/j.neuron.2016.03.005
- Umeda, T., Mori, H., Zheng, H., and Tomiyama, T. (2010). Regulation of cholesterol efflux by amyloid beta secretion. *J. Neurosci. Res.* 88, 1985–1994. doi: 10.1002/jnr.22360
- Umeda, T., Tomiyama, T., Sakama, N., Tanaka, S., Lambert, M. P., Klein, W. L., et al. (2011). Intraneuronal amyloid beta oligomers cause cell death via endoplasmic reticulum stress, endosomal/lysosomal leakage, and mitochondrial dysfunction in vivo. *J. Neurosci. Res.* 89, 1031–1042. doi: 10.1002/jnr.22640

- van der Kant, R., Langness, V. F., Herrera, C. M., Williams, D. A., Fong, L. K., Leestemaker, Y., et al. (2019). Cholesterol Metabolism Is a Druggable Axis that Independently Regulates Tau and Amyloid-beta in iPSC-Derived Alzheimer's Disease Neurons. *Cell Stem Cell* 24, 363–375.e9. doi: 10.1016/j.stem.2018.12.013
- van Oijen, M., Hofman, A., Soares, H. D., Koudstaal, P. J., and Breteler, M. M. (2006). Plasma Abeta(1-40) and Abeta(1-42) and the risk of dementia: A prospective case-cohort study. *Lancet Neurol* 5, 655–660. doi: 10.1016/s1474-4422(06)70501-4
- Vandenbergh, R., Riviere, M. E., Caputo, A., Sovago, J., Maguire, R. P., Farlow, M., et al. (2017). Active Abeta immunotherapy CAD106 in Alzheimer's disease: A phase 2b study. *Alzheimers Dement* 3, 10–22. doi: 10.1016/j.trci.2016.12.003
- Venegas, C., Kumar, S., Franklin, B. S., Dierkes, T., Brinkschulte, R., Tejera, D., et al. (2017). Microglia-derived ASC specks cross-seed amyloid-beta in Alzheimer's disease. *Nature* 552, 355–361. doi: 10.1038/nature25158
- Vinters, H. V. (2015). Emerging concepts in Alzheimer's disease. *Annu. Rev. Pathol.* 10, 291–319. doi: 10.1146/annurev-pathol-020712-163927
- Walker, J. R., Pacoma, R., Watson, J., Ou, W., Alves, J., Mason, D. E., et al. (2013). Enhanced proteolytic clearance of plasma Abeta by peripherally administered neprilysin does not result in reduced levels of brain Abeta in mice. *J. Neurosci.* 33, 2457–2464. doi: 10.1523/jneurosci.3407-12.2013
- Walti, M. A., Ravotti, F., Arai, H., Glabe, C. G., Wall, J. S., Böckmann, A., et al. (2016). Atomic-resolution structure of a disease-relevant Abeta(1-42) amyloid fibril. *Proc. Natl. Acad. Sci. U. S. A.* 113, E4976–E4984. doi: 10.1073/pnas.1600749113
- Wang, D. S., Iwata, N., Hama, E., Saido, T. C., and Dickson, D. W. (2003). Oxidized neprilysin in aging and Alzheimer's disease brains. *Biochem. Biophys. Res. Commun.* 310, 236–241. doi: 10.1016/j.bbrc.2003.09.003
- Wang, J., Gu, B. J., Masters, C. L., and Wang, Y. J. (2017). A systemic view of Alzheimer disease - insights from amyloid-beta metabolism beyond the brain. *Nat. Rev. Neurol.* 13, 612–623. doi: 10.1038/nrneurol.2017.111
- Wang, Q. H., Wang, Y. R., Zhang, T., Jiao, S. S., Liu, Y. H., Zeng, F., et al. (2016). Intramuscular delivery of p75NTR ectodomain by an AAV vector attenuates cognitive deficits and Alzheimer's disease-like pathologies in APP/PS1 transgenic mice. *J. Neurochem.* 138, 163–173. doi: 10.1111/jnc.13616
- Wang, Y. J. (2014). Alzheimer disease: Lessons from immunotherapy for Alzheimer disease. *Nat. Rev. Neurol.* 10, 188–189. doi: 10.1038/nrneurol.2014.44
- Wang, Z., Natta, R., Berliner, J. A., van Duinen, S. G., and Vinters, H. V. (2000). Toxicity of Dutch (E22Q) and Flemish (A21G) mutant amyloid beta proteins to human cerebral microvessel and aortic smooth muscle cells. *Stroke* 31, 534–538. doi: 10.1161/01.str.31.2.534
- Watts, J. C., Condello, C., Stöhr, J., Oehler, A., Lee, J., DeArmond, S. J., et al. (2014). Serial propagation of distinct strains of Abeta prions from Alzheimer's disease patients. *Proc. Natl. Acad. Sci. U. S. A.* 111, 10323–10328. doi: 10.1073/pnas.1408900111
- Wegiel, J., Wang, K. C., Imaki, H., Rubenstein, R., Wronska, A., Osuchowski, M., et al. (2001). The role of microglial cells and astrocytes in fibrillar plaque evolution in transgenic APP(SW) mice. *Neurobiol. Aging* 22, 49–61. doi: 10.1016/s0197-4580(00)00181-0
- Welander, H., Fränberg, J., Graff, C., Sundström, E., Winblad, B., and Tjernberg, L. O. (2009). Abeta43 is more frequent than Abeta40 in amyloid plaque cores from Alzheimer disease brains. *J. Neurochem.* 110, 697–706. doi: 10.1111/j.1471-4159.2009.06170.x
- Wijesekara, N., Ahrens, R., Sabale, M., Wu, L., Ha, K., Verdile, G., et al. (2017). Amyloid-beta and islet amyloid pathologies link Alzheimer's disease and type 2 diabetes in a transgenic model. *FASEB J.* 31, 5409–5418.1. doi: 0.1096/fj.201700431R
- Winblad, B., Andreasen, N., Minthon, L., Floesser, A., Imbert, G., Dumortier, T., et al. (2012). Safety, tolerability, and antibody response of active Abeta immunotherapy with CAD106 in patients with Alzheimer's disease: Randomised, double-blind, placebo-controlled, first-in-human study. *Lancet Neurol* 11, 597–604. doi: 10.1016/s1474-4422(12)70140-0
- Wraith, D. C., and Nicholson, L. B. (2012). The adaptive immune system in diseases of the central nervous system. *J. Clin. Invest.* 122, 1172–1179. doi: 10.1172/jci58648
- Xie, C., Soeda, Y., Shinzaki, Y., In, Y., Tomoo, K., Ihara, Y., et al. (2015). Identification of key amino acids responsible for the distinct aggregation properties of microtubule-associated protein 2 and tau. *J. Neurochem.* 135, 19–26. doi: 10.1111/jnc.13228
- Xie, L., Helmerhorst, E., Taddei, K., Plewright, B., Bronswijk, W. V., and Martins, P. (2002). Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. *J. Neurosci.* 22:RC221. doi: 10.1523/JNEUROSCI.22-10-j0001.2002
- Yamada, M., and Naiki, H. (2012). Cerebral amyloid angiopathy. *Prog. Mol. Biol. Transl. Sci.* 107, 41–78. doi: 10.1016/b978-0-12-385883-2.00006-0
- Yan, R., and Vassar, R. (2014). Targeting the beta secretase BACE1 for Alzheimer's disease therapy. *Lancet Neurol* 13, 319–329. doi: 10.1016/s1474-4422(13)70276-x
- Yao, X. Q., Jiao, S. S., Saadipour, K., Zeng, F., Wang, Q. H., Zhu, C., et al. (2015). p75NTR ectodomain is a physiological neuroprotective molecule against amyloid-beta toxicity in the brain of Alzheimer's disease. *Mol. Psychiat.* 20, 1301–1310. doi: 10.1038/mp.2015.49
- Yasojima, K., McGeer, E. G., and McGeer, P. L. (2001). Relationship between beta amyloid peptide generating molecules and neprilysin in Alzheimer disease and normal brain. *Brain Res.* 919, 115–121. doi: 10.1016/s0006-8993(01)03008-6
- Yin, K. J., Cirrito, J. R., Yan, P., Hu, X., Xiao, Q., Pan, X., et al. (2006). Matrix metalloproteinases expressed by astrocytes mediate extracellular amyloid-beta peptide catabolism. *J. Neurosci.* 26, 10939–10948. doi: 10.1523/jneurosci.2085-06.2006
- Yoon, S. S., and Jo, S. A. (2012). Mechanisms of Amyloid-beta Peptide Clearance: Potential Therapeutic Targets for Alzheimer's Disease. *Biomol. Ther.* 20, 245–255. doi: 10.4062/biomolther.2012.20.3.245
- Yu, Y., Jans, D. C., Winblad, B., Tjernberg, L. O., and Schedin-Weiss, S. (2018). Neuronal Abeta42 is enriched in small vesicles at the presynaptic side of synapses. *Life Sci. Alliance* 1:e201800028. doi: 10.26508/lsa.201800028
- Zare-Shahabadi, A., Masliah, E., Johnson, G. V., and Rezaei, N. (2015). Autophagy in Alzheimer's disease. *Rev. Neurosci.* 26, 385–395. doi: 10.1515/revneuro-2014-0076
- Zhang, K., Sun, Z., Chen, X., Zhang, Y., Guo, A., and Zhang, Y. (2021). Intercellular transport of Tau protein and  $\beta$ -amyloid mediated by tunneling nanotubes. *Am. J. Transl. Res.* 13, 12509–12522.
- Zhang, L., Sheng, R., and Qin, Z. (2009). The lysosome and neurodegenerative diseases. *Acta Biochim. Biophys. Sin.* 41, 437–445. doi: 10.1093/abbs/gmp031
- Zhang, Y., Guo, O., Huo, Y., Wang, G., and Man, H. Y. (2018). Amyloid-beta Induces AMPA Receptor Ubiquitination and Degradation in Primary Neurons and Human Brains of Alzheimer's Disease. *J. Alzheimers Dis.* 62, 1789–1801. doi: 10.3233/jad-170879
- Zhang, Y., Zhou, B., Deng, B., Zhang, F., Wu, J., Wang, Y., et al. (2013). Amyloid-beta induces hepatic insulin resistance in vivo via JAK2. *Diabetes* 62, 1159–1166. doi: 10.2337/db12-0670
- Zhang, Y., Zhou, B., Zhang, F., Wu, J., Hu, Y., Liu, Y., et al. (2012). Amyloid-beta induces hepatic insulin resistance by activating JAK2/STAT3/SOCS-1 signaling pathway. *Diabetes* 61, 1434–1443. doi: 10.2337/db11-0499
- Zhang, Y. W., Thompson, R., Zhang, H., and Xu, H. (2011). APP processing in Alzheimer's disease. *Mol. Brain* 4:3. 6606-4-3 doi: 10.1186/1756-
- Zhao, J., Nussinov, R., and Ma, B. (2017). Mechanisms of recognition of amyloid-beta (Abeta) monomer, oligomer, and fibril by homologous antibodies. *J. Biol. Chem.* 292, 18325–18343. doi: 10.1074/jbc.M117.801514
- Zhao, W. Q., De Felice, F. G., Fernandez, S., Chen, H., Lambert, M. P., Quon, M. J., et al. (2008). Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J.* 22, 246–260. doi: 10.1096/fj.06-7703com
- Zheng, L., Cedazo-Minguez, A., Hallbeck, M., Jerhammar, F., Marcusson, J., and Terman, A. (2012). Intracellular distribution of amyloid beta peptide and its relationship to the lysosomal system. *Transl. Neurodegener.* 1:19. doi: 10.1186/2047-9158-1-19
- Zhou, R., Deng, J., Zhang, M., Zhou, H. D., and Wang, Y. J. (2011). Association between bone mineral density and the risk of Alzheimer's disease. *J. Alzheimers Dis.* 24, 101–108. doi: 10.3233/jad-2010-101467
- Zhu, J., Wang, Y., Li, J., Deng, J., and Zhou, H. (2014). Intracranial artery stenosis and progression from mild cognitive impairment to Alzheimer disease. *Neurology* 82, 842–849. doi: 10.1212/wnl.0000000000000185
- Zlokovic, B. V. (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat. Rev. Neurosci.* 12, 723–738. doi: 10.1038/nrn3114