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# Chemical Modulation of Amyloid Beta Oligomer's in Alzheimer's Disease

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## ABSTRACT

Amyloid beta oligomers play a key role in the pathophysiology of Alzheimer's disease. Since it contributes to memory and neuronal loss, cognitive decline, degradation of neurons as well as diseases progression. As Aβ oligomer is very small and heterogeneous and it can change from one shape to another shape therefore it has various kinds of morphologies including monomers, oligomers and fibrils. Due to instable behavior of these proteins, it's very difficult to understand its exact mechanism. In this concise review, information over the past seven years concentrated on the molecular characteristics of amyloid-β oligomers has been summarized along with two pathways involving protein aggregation and condensation. Furthermore, metal complexes, immunotherapies, and anti-Aβ antibodies are reported here, which can modulate aggregation, stabilize non-toxic forms, and enhance degradation. Finally, new discoveries on small molecules that control, modify and inhibit the progression of amyloid-β oligomers are integrated, as these are key characteristics of Alzheimer's disease.

## INTRODUCTION

According to recent projections, the number of people living with Alzheimer disease (AD), the most prevalent form of dementia, is expected to reach 87 million by 2050. Age is the primary risk factor for AD, which currently affects more than 35 million people worldwide (Hwang *et al.*, 2019; Tzioras *et al.*, 2022). Given that 50–80% of all cases among the elderly population are estimated to be related to this rapidly ageing population, it has emerged as a significant social issue (Peng *et al.*, 2019). Aberrant protein aggregation, which affects synaptic signaling, mitochondrial function, neuroinflammation, and neuronal loss, is indicative of AD and leads to multifactorial neuronal dysfunction (Limbocker *et al.*, 2019). Alzheimer's disease (AD) is caused by misfolded tau and amyloid-beta (Aβ) proteins that build up in the brain along harmful pathways that cause selective neuronal death and synaptic loss (Figure 1) (Senapati *et al.*, 2023). The primary neurotoxic species responsible for the onset of Alzheimer's disease (AD) are oligomeric aggregates of amyloid-β peptides (Aβ). Aβ oligomers stimulate additional pathological processes of AD, including tau hyperphosphorylation, oxidative stress, and mitochondrial dysfunction, in addition to causing various neuronal dysfunctions like loss of memory and learning. Thus, it is acknowledged that Aβ oligomers are suitable targets for AD diagnosis and treatment (Sehar *et al.*, 2022). In the pathophysiology of AD and other tauopathies, tauOs and tau filaments may be crucial players. The general consensus is that smaller, diffusible oligomers are more likely to be involved in AD pathogenesis than the larger tau assemblies, which include straight filaments, PHF, NFT, and ghost tangles, which are thought to be less toxic (Penke *et al.*, 2020). Compared to amyloid fibrils, soluble Aβ oligomers have a stronger correlation with the advancement of disease. For this reason, focusing on these oligomers may prove to be a useful therapeutic approach in the management and prevention of Alzheimer's (Jehangir *et al.*, 2024). Finding Aβo in biological samples, like blood or cerebrospinal fluid, has enormous potential for tracking the development of AD and providing an early diagnosis. But because Aβo are dynamic, structurally complex, and rare, it's still very difficult to detect them accurately (Penke *et al.*, 2020). Many of these disease-associated proteins not only misfold and aggregate, but also go through liquid-liquid phase separation (LLPS) to create dynamic condensates, which are essential for regular cellular processing (Muhammad *et al.*, 2024). Many studies suggest that LLPS plays a significant role in the deposition and aggregation of tau and amyloid-β and is closely linked to the pathophysiology of AD. Investigating the fundamental mechanism in greater detail will help increase the rate of early AD detection, which will lead to the development of anti-AD medications and better outcomes for AD patients (Muhammad *et al.*, 2024). In this concise review, we gathered information over the past seven years and concentrated on the molecular characteristics of amyloid-β oligomers, along with two pathways involving protein aggregation and condensation. We also integrated new discoveries on small molecules that control, modify, and break down amyloid-β oligomers, which are key characteristics of Alzheimer's disease. Finally, we touched on their roles in the pathophysiology of the disease. It is known that Aβ oligomers are the target of studies on chemical regulatory mechanisms, stabilization, and degradation processes, as well as the role of phase separation in Alzheimer's disease.

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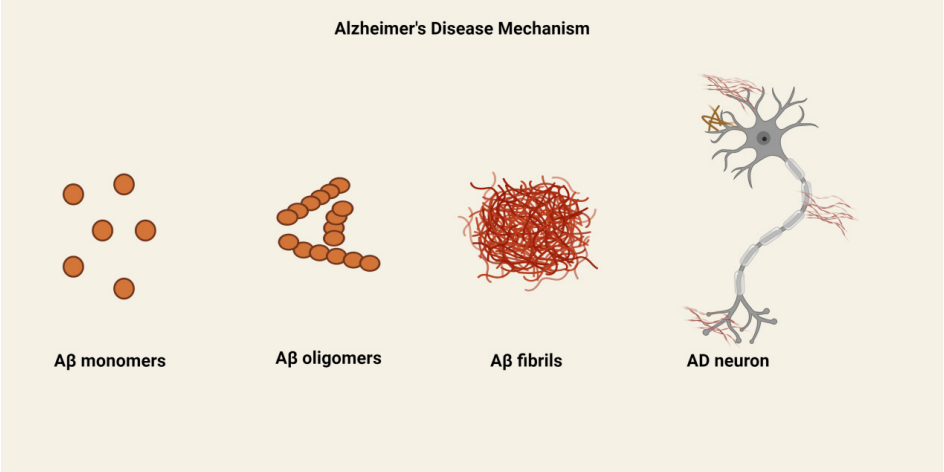



**Figure 1:** Amyloid-β (Aβ) misfolds and forms soluble toxic oligomers and fibrils that accumulate in the brain leading to synaptic loss and selective neuronal death

## LITERATURE REVIEW

### Amyloid-β Oligomers, Protein Aggregation and Condensation

Soluble AβO can start to accumulate in the brain up to two decades before clinical symptoms appear (Hector & Brouillette, 2021). Aβ is produced as a result of the amyloid precursor protein's proteolytic cleavage by β- and γ-secretases. The two most prevalent forms of Aβ in human bodies are Aβ40 and Aβ42. Aβ42 was found to be more likely to aggregate, despite the fact that Aβ40 and Aβ42 only differ by two amino acid residues. Aβ has a tendency to form a variety of self-assembly structures, from mature fibrils to oligomers and as well as monomer's (Volynsky *et al.*, 2025). Aβ toxicity has been shown to be primarily caused by Aβ1~42 oligomers, both in vitro and in vivo (Han *et al.*, 2025). Experimentally and computationally characterizing the early Aβ oligomers is a difficult task. Since most experimental observations provide time- and space-averaged properties, the transient and heterogeneous ensemble of oligomer structures presents an experimental challenge (Derreumaux *et al.*, 2022). At physiological concentrations of 1–20 nM, Aβ42 synthesis easily forms oligomeric structures, and the rate of oligomer formation is temperature-dependent. At physiological concentrations, the formation of Aβ42 oligomers is a kinetically analyzed and inhibitable process that is repeatable (Li *et al.*, 2023). The most neurotoxic agents are thought to be Aβ42 oligomers. The morphologies of these oligomeric intermediates are diverse, encompassing spherical, annular, β-barrel, and protofibrillar forms, all of which have the potential to contribute differently to the toxicity of Aβ (Foley *et al.*, 2019). In order to diagnose and treat AD, Aβ oligomers are accepted as valid targets. However, because the term "Aβ oligomer" can refer to a variety of soluble Aβ species or a mixture of different types of metastable oligomeric species with different sizes, shapes, and conformations as a result of Aβ's dynamic assembly, it can be somewhat ambiguous (Viola & Klein, 2015). Various experiments have contributed to our current understanding of the structures and biology of Aβ oligomers, even though a unified model for their role in Alzheimer's disease has not yet been developed. Studies using solid-state nuclear magnetic resonance (NMR) conducted by Paravastu and colleagues revealed that antiparallel β-sheets make up the oligomers of Aβ (Haerianardakani *et al.*, 2020).

### Protein Aggregation and Condensation

The word "aggregation" is frequently used in biology to refer to assemblies that are created under pathological circumstances, where the molecules within the aggregate are irreversibly disrupted and frequently regarded as pathogenic factors. One important feature of biological processes that are irreversible is aggregation. In contrast, the word "condensation" describes dynamic, reversible molecules that can be redissolved to carry out their specific tasks; the intracellular environment is closely monitored during their assembly (Alberti & Hyman, 2021). But there is some degree of interdependence between these two categories of higher-order protein assemblers. Protein components can misfold and irreversibly aggregate when protein homeostasis is disrupted under pathological or pressure conditions, which can lead to an imbalance in biomolecular condensation and the uncontrollable collapse of these structures. Aging or solidified condensates can then frequently transform into aggregates (Amzallag & Hornstein, 2022; Savastano *et al.*, 2020). Protein condensates or aggregates may arise from intermediate clusters as precursors of droplets or aggregates under certain circumstances. A droplet that forms as an intermediate aggregate and then transforms into a solid state is one more potential mechanism for protein aggregation (Wegmann *et al.*, 2018). Nonetheless, a number of investigations have indicated that amyloid (or cross-β) interactions play a role in the development of protein aggregates, and the in vitro production of amyloid fibrils is commonly observed in phase-separated proteins (Hughes *et al.*, 2018; Luo *et al.*, 2018). Aside from nervous system conditions like schizophrenia, bipolar, and autism disorders, depression, epilepsy, and

Alzheimer's and Parkinson's diseases, the top-ranking protein condensation diseases also include depression. Synaptic condensate-forming proteins' genes are linked to the majority of these neurological disorders (Zeng *et al.*, 2016). The growing body of evidence indicates that a variety of human diseases are probably caused by aberrant protein condensation. Changes in the physiological states of proteins are the root cause of these pathologies, which are collectively known as protein condensation diseases (Li *et al.*, 2020). Yet, nucleation and off-pathway aggregation are frequently involved in the formation of amyloid fibrils, which is not just a straightforward polymerization process. Delays cause disordered intermediates to refold into non-native secondary structures (β-strands), which are linked to the creation of oligomers, during a lag phase. In certain cases, during the α-β structure transition, folding intermediates with extended (non-native) α-helices can form native or amyloid states (Žerovnik & Venko, 2023). Because of the stacking of aromatic rings and a network of backbone hydrogen bonds, amyloid fibrils, which are highly ordered and rigid protein states, can have a variety of morphologies (Stanković *et al.*, 2020; Taylor & Staniforth, 2022). Reversibility is one of the main distinctions between protein condensates and aggregates. Protein condensates are at least initially reversible, in contrast to more toxic forms of protein aggregates (Shin *et al.*, 2017). A characteristic of diseases like transmissible spongiform encephalopathies, prion diseases, Alzheimer's disease, and Parkinson's disease is protein aggregation. There is ongoing debate as to whether the aggregated proteins are involved in the pathological process directly or are merely bystanders. Consequently, it is crucial to comprehend PS and aggregation. It is becoming evident that the pathogenesis of neurodegenerative disorders may involve proteins with liquid-to-solid transitions, such as Tau, α-synuclein, and TDP-43, which bind to RNA and are fused in sarcoma (FUS) (Zbinden *et al.*, 2020). The discovery of liquid-like condensates raises the prospect of a different route for amyloid aggregation. This "condensation pathway" is different from the "deposition pathway," which is the direct formation of amyloid aggregates from their native state via oligomeric species. Even within the same cell and protein system going through self-assembly, solid deposits have been seen to form either directly through the deposition pathway or from liquid droplets through the condensation pathway (Cascella *et al.*, 2022; Hardenberg *et al.*, 2020). However, when amyloid aggregation occurs within condensates, the role of oligomers is still unclear. Within a condensed gel-like phase, it was discovered that TDP-43 oligomers form in both the deposition and condensation pathways and before solid aggregates emerge (French *et al.*, 2019). Furthermore, it has been documented that α-synuclein oligomers were formed right after the monomeric protein underwent phase separation into a hydrogel. In this environment, monomers, oligomers, and fbrils coexist, and the hydrogels trap α-synuclein in a highly cytotoxic state rather than releasing it (Kumar *et al.*, 2018). Similarly, it was discovered that liquid–liquid phase separation causes a pathogenic conformation and oligomerization in tau and comes before gel formation and subsequently aggregation in vitro (Kanaan *et al.*, 2020; Wegmann *et al.*, 2018).

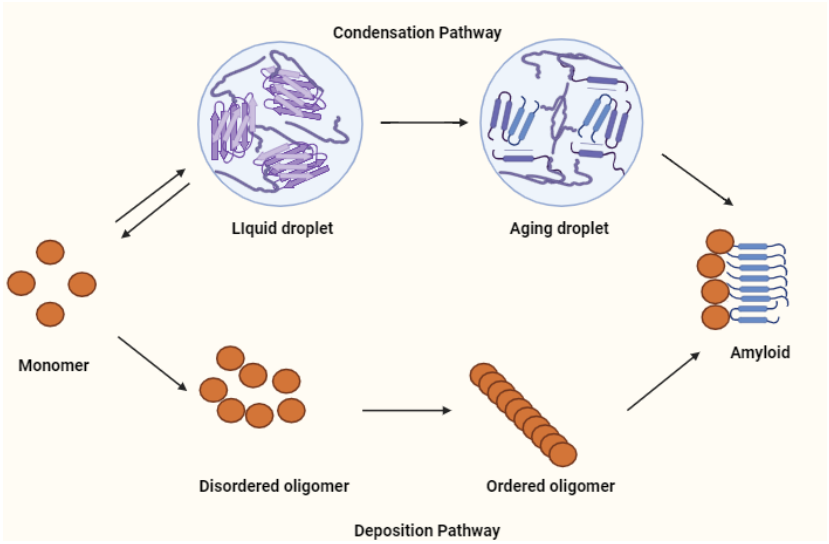
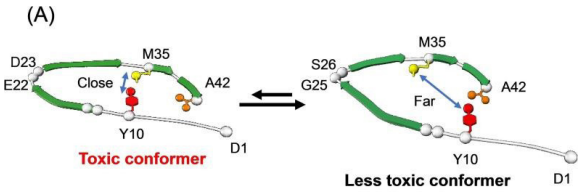


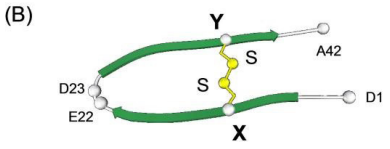

**Figure 2:** A synopsis of condensation and the amyloid formation deposition pathway.
*Source: BioRender*

**Structural Features**

Understanding the intricate structure of Aβ(1-42) oligomer's is crucial, and in recent times, solid-state NMR-spectroscopy has been used to perform structural analyses on various oligomer preparations of Aβ(1-42) oligomer's and Aβ(1-40)oligomer's (also known as pyro-Glu-Aβ(3/11–40) oligomers)(König *et al.*, 2021). Both on-pathway precursor and off-pathway competitors can be acted upon by the oligomers during the oligomer to mature fibril conversion for Aβ42. Mostly composed of residue Aβ peptide species, these fibrils have well-known structures. The β-strands of these firbils are oriented perpendicularly to the fibril axis, giving them a general appearance of cross-shaped β structure. Two

hydrophobic β-sheet segments with an in-register orientation and parallel orientation are present in these fibrils, despite their unstructured N-terminus (Saha & Jana, 2022). In order to examine the biological activities of Aβ oligomers and evaluate their physicochemical and structural characteristics, various techniques have been devised to produce oligomers that are relatively stable and do not easily transform into amyloid fibrils. Aβ oligomers that are frequently employed in the examination of animal and cellular models of Alzheimer's disease are Aβ-derived diffusible ligands, or ADDLs (Jang *et al.*, 2023). The toxic conformer of Aβ42, with a turn at positions 22/23, and the less toxic conformer, with a turn at positions 25/26, were identified (Figure 3A) through systematic proline replacement and analyses using solid-state nuclear magnetic resonance (NMR) spectroscopy and electron spin resonance (ESR) to gather information on the secondary structure of Aβ42 oligomers and fibrils. The turn at positions 22/23 is one of the important secondary structures of Aβ42 for cytotoxicity and aggregative ability, as was previously mentioned. We performed cross-linking of the residues located at Aβ42 positions 21/24, 19/26, 17/28, 15/30, and 13/32. An intramolecular disulfide bond at positions 17/28 is present in the Aβ42 analogue (Figure 3) (Matsushima *et al.*, 2022).




| Analog | X | Y |
|---|---|---|
| 1 | L17C | K28C |
| 2 | L17homoCys | K28C |
| 3 | L17C | K28homoCys |
| 4 | L17homoCys | K28homoCys |
| 5 | K16C | G29C |
| 6 | V18C | N27C |

**Figure 3:** (A) Structure of toxic and less toxic conformers with a turn at positions 22/23 and 25/26, respectively.20 (B) Structure of cross-linked Aβ42 analogues (1–6). Adopted from Ref (Matsushima *et al.*, 2022)

### Role in Alzheimer's Pathology

It is widely acknowledged that AβOs are important players in the pathogenetic mechanisms of AD because of their capacity to cause neurotoxicity, synaptotoxicity, and neuroinflammation, and because these effects can explain the neuropathological characteristics of AD. Mixtures of diverse species, varying in size from tiny to large, make up AβOs; however, it is still unclear which species are the most toxic (Araki, 2023). Our findings, along with numerous other in vitro and in vivo investigations, corroborate the notion that AβOs cause a range of pathological changes, such as oxidative stress, mitochondrial dysfunction, synaptic deficits, apoptosis, aberrant tau alterations, and cognitive impairments (Araki & Kametani, 2022) Aβ oligomers may be involved in AD pathology in a number of ways, such as neuronal toxicity and excitotoxicity caused by constriction of brain blood vessels due to increased calcium levels. AD can start in vivo and in vitro when small soluble Aβ1-42 oligomers cause neurotoxicity. For this reason, it is currently thought that Aβ oligomers are more neurotoxic and disease-relevant than Aβ fibrils (Matuszyk *et al.*, 2021). When AβOs binds to different receptors on the surface of neurons, it can interfere with signaling pathways and cause cells to die. AβOs recognizes more than 20 receptors, such as β7nAChR, p75NTR, PrPc, glutamate receptors, and β2-AR. APP intracellular domain (AICD) production is decreased and β-secretase activity is inhibited by PrPc, an important protein that regulates Aβ metabolism in vivo under normal physiological conditions. Aβos, on the other hand, binds to PrPc and interferes with its normal physiological functions in AD brains (Huang & Liu, 2020). The majority of scientists believe that Aβ oligomers cause synaptotoxicity by activating metabotropic glutamate receptor type 5 (mGluR5) and stimulating three kinases that inhibit LTP: c-Jun N-terminal protein kinase 1, JNK1; cyclin-dependent kinase 5, Cdk5; and p38 mitogen-activated protein kinase, p38 MAPK (Diociaiuti *et al.*, 2021). The species most closely linked to the pathophysiology of AD are soluble Aβ oligomers, which can be found in APP transgenic mice, AD patients, vitro, and in vivo in a wide variety of forms. These diverse Aβ oligomer types show their neurotoxic effects in AD via multiple distinct mechanisms (Madhu & Mukhopadhyay, 2021). The toxic influence of AβOs has been extensively studied in transgenic animal models, AD brain tissues, and cell cultures. Numerous studies have shown that amyloid oligomers of different origins can cause alterations in neurons. AβOs isolated from the brains of AD patients or animal models of the disease, as well as synthetic peptides or Aβ species secreted in cultured cells (Mroczko *et al.*, 2017). In summary, AβOs have been observed to trigger tau pathology, axonal transport impairment, loss of neuronal polarity, oxidative stress, endoplasmic reticulum (ER) stress, deterioration of synapses, insulin resistance, neuroinflammation, cholinergic impairment, loss of trophic factors, epigenetic modifications, ectopic mitosis, and selective death of nerve cells (Cline *et al.*, 2018).

Chemical regulation of amyloid-β oligomerization

Alzheimer's disease and related illnesses are characterized by a pathogenic process called amyloid-beta aggregation. in order to develop effective treatments (Cline *et al.*, 2018). Understanding how this aggregation is made is crucial. Treatment options include GAL-201, which is thought

to bind preferentially to mis-folded Aβ1-42 monomers. This high-affinity binding prevents larger aggregates and harmful oligomers from forming by interfering with the aggregation process. Through its ability to inhibit Aβ aggregation, GAL-201 may be able to prevent or slow the onset of amyloid-beta-related neurodegenerative diseases, such as Alzheimer's (Russ *et al.*, 2022). There are now multiple strategies to combat the Alzheimer's-related Aβ assemblies (Fish *et al.*, 2019). Immunotherapeutic vaccinations, antibodies, peptides, and nanoparticles are a few of the tactics. Many compounds, such as Congo red, LPFFD, myricetin, melatonin, 9,10-anthraquinone, trehalose, Thioflavin T, N-methylated peptides, polyphenol EGCG, ibuprofen, naproxen, morin, and particular polyphenolic compounds, have shown promise in blocking Aβ aggregation and upsetting beta sheet structures (Grasso & Danani, 2020). Plants like berries and grapes contain a polyphenolic flavonoid called myricetin, which has a variety of biological activities such as antibacterial, anti-inflammatory, and antioxidant properties. Inhibition of Aβ oligomerization by myricetin has also been demonstrated (Araki & Kametani, 2022). Anti-Aβ monoclonal antibodies have the ability to stop Aβ monomers from forming fibrillar aggregates in vitro and to change fibrillar aggregates into an amorphous form. It's interesting to note that these mechanisms' effectiveness is influenced by antibody concentration (Mantile & Prisco, 2020) . There have been reports of certain anti-Aβ antibodies binding directly to Aβ, which either dissolve Aβ aggregates in vitro or prevents Aβ from oligomerizing and forming fibrils. Particular Aβ antibodies with specific conformations target pre-existing brain plaques and cause direct in vivo disintegration. According to these results, Aβ aggregation may be impacted by the direct interaction of anti-Aβ antibodies with Aβ in both vitro and in vivo settings (Liu *et al.*, 2025). A phase III clinical trial for four monoclonal anti-Aβ antibodies—adecaluzumab, BAN2401, gantenerumab, and solanezumab—has begun, according to a recent study. Aducanumab is a human IgG1 antibody that targets only soluble oligomers and insoluble fibrils of Aβ. It was chosen through memory B cell screening in healthy elderly individuals (Panza *et al.*, 2025). The FDA has recently approved it as an immunotherapy for AD. Aducanumab (BIIB037) is a monoclonal antibody of human IgG1 that forms an extended conformation with the N terminus of Aβ. It targets aggregates of Aβ, including insoluble fibrils and soluble oligomers (Song *et al.*, 2022). Using molecular docking, the virtual peptide P21 is able to effectively inhibit the aggregation of Aβ1-42 proteins, thereby decreasing neurotoxicity (Wu *et al.*, 2023). Two classes of poly-phenols inhibit the aggregation of Aβ in distinct ways. On the one hand, flavonoids led to the formation of spherical, unstructured aggregates and completely inhibited the fibrillation of Aβ monomers. Conversely, stilbenes suppressed Aβ aggregation, although to a much smaller degree. Remarkably, the common stilbene resveratrol speed up the production of Aβ fibrils (Phan *et al.*, 2019). Metal ions have been shown to either accelerate or slow down Aβ aggregation based on the total metal ion concentration and metal:Aβ ratio, as has been covered in multiple review articles. While it has been demonstrated that Cu (II), Zn(II), and Ag(I) slow down Aβ fibrillization at low metal ion concentrations, Aβ aggregation can be stimulated at high concentrations, leading to the formation of amorphous aggregates.

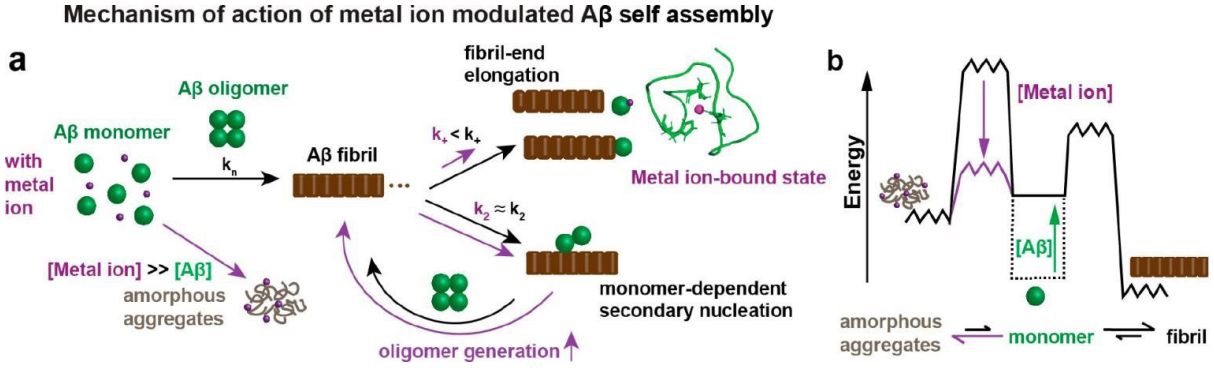



**Figure 4:** Model for mechanism of action of metal ion-modulated Aβ self-assembly

Transition-metal ions, in particular referring to Cu (II), Zn(II), and Ag(I) ions, specifically prevent fibril-end elongation events by forming a seemingly aggregation-inert metal-bound Aβ complex. Inhibition of fibril elongation predicts an enhanced rate of oligomer generation. At high metal ion concentration, other aggregation processes dominate, and amorphous aggregates are formed. (b) An energy diagram shows the concentration-dependent formation of Aβ fibrils and amorphous Aβ aggregates, where an increased concentration of Aβ generally enhances aggregation and the energy barrier toward amorphous aggregate formation is determined by the metal ion concentration. Copy from ref (Abelein, 2023).

Metal ions, particularly Zn2+ and Cu2+, have a strong affinity for binding to Aβ, which can facilitate Aβ nucleation and aggregation (Rana & Sharma, 2019). According to a recent study, quinoline-derived half-curcumin dioxaborine (Q-OB) was made in order to identify the early stage of AD by detecting the oligomeric Aβ1-42 over monomer and filaments in the complex Aβ self-assembly cascade. In AD transgenic mice, Q-OB

demonstrated exceptional blood-brain barrier (BBB) penetrability and in vivo imaging of Aβ (An *et al.*, 2024). The studies of anti-Aβ 3D6 antibody is said to stop the development of new Aβ plaques in the brain, but it doesn't eliminate those that already exist. Additionally, 3D6 inhibited the aggregation of Aβ (Amano *et al.*, 2023). The relationships between the Aβ peptide and the main Aβ aggregation inhibitors, geraniin (1), gallic acid (2), and corilagin (5), were investigated using STD NMR spectra. This study implies that smaller soluble Aβ aggregates are inhibited by corilagin (5), whereas larger insoluble Aβ aggregates are inhibited by gallic acid (2). Corilagin (5) only interacts with soluble Aβ, as demonstrated by this as well (Kubo *et al.*, 2022). Certain classes, like polyphenols and tetracyclines, can prevent the aggregation of various unrelated amyloidogenic proteins, like islet amyloid polypeptide (IAPP), which is linked to type-2 diabetes, and α-synuclein, which is linked to Parkinson's disease. It's likely that their mechanisms of action are partially overlapped (Martinez Pomier *et al.*, 2020). Many in vitro and in vivo investigations have demonstrated the potential of a variety of natural compounds as therapeutic agents against the progression of AD however, pre-clinical and clinical studies have only demonstrated the efficacy of a small subset of these compounds (Andrade *et al.*, 2019). After being extracted from red maples, ginsenalin A (GA) can target Aβ42 fibrillogenesis through a variety of mechanisms. Specifically, GA can bind to monomers at the early nucleation phase, preventing Aβ–Aβ associations, and at the later growth phase. According to toxicity tests on SH-SY5Y cells, pre-incubation of Aβ42 solution with GA results in oligomers that do not interact or disturb the integrity of cellular membranes (Pagano *et al.*, 2020). Further evidence suggests that the antioxidant ferrulic acid (FA), which is found in plant cell walls, may inhibit the aggregation of Aβ (Thapliyal *et al.*, 2021). The biomolecular targets linked to Alzheimer's disease (AD) include the NMDA receptor, Aβ aggregation, AChE, and monoamine oxidase (MAO) (Uddin *et al.*, 2020). (Figure 5) shows how harmine and its derivatives bind to numerous targets. Harmine treatments decrease scopolamine-induced cognitive impairment in mice and enhance spatial learning, memory in transgenic mice, short-term memory in aged rats, and all of these outcomes. This illustrates how harmine targets different aspects of the disease and has the potential to be a multimodal treatment for Alzheimer's (Du *et al.*, 2023). Study investigated the potential therapeutic effects of GnRb1, SA, and DMyr on Aβ aggregation in AD. Our study suggests that since SA, GnRb1, and DMyr target Aβ aggregation, they might be appealing treatment options for AD based on the amyloid hypothesis (Sharari *et al.*, 2023). By significantly binding to Aβ oligomers and monomers, the nanoparticles (NP@ SiO2@F-SLOH) reduce Aβ aggregation, as confirmed by the ThT fluorescence experiment. This suggests the potential for Alzheimer's disease (AD) treatment. Aβ species ranging from Aβ42 monomers and oligomers to Gd3+-based NPs with F-SLOH surface functionalization lessen neurotoxicity as well. Additionally, the NPs effectively stop Aβ species from generating reactive oxygen species (ROS), indicating that AD treatments may be possible with them (Wang *et al.*, 2020).

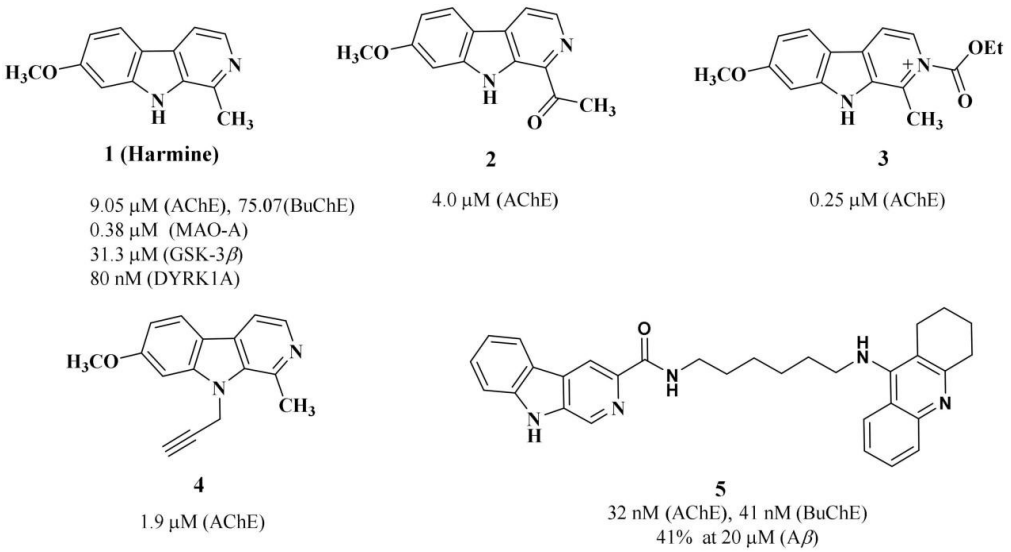



**Figure 5:** Chemical structures of harmine and its derivatives. Copy from ref (Du *et al.*, 2023)

**Stabilization of Amyloid-β Oligomers**

A number of tiny compounds have been demonstrated to be useful anti-aggregating agents in the treatment of Alzheimer's disease, including curcumin, resveratrol, ellagic acid, meric decapeptide rk10, and epigallocatechin-3-gallate (EGCG) (Mohammed *et al.*, 2023). The active polyphenol found in green tea, called epigallocatechin-3-gallate (EGCG), has drawn a lot of interest because of its potential for health benefits, which include anti-oxidation, radical scavenging, metal chelating, anti-carcinogen, anti-apoptosis, and anti-inflammatory qualities (Mokra *et al.*, 2022). EGCG activates the proteolytic pathway of nonamyloidogenic α-secretase, which inhibits the aging process of the brain and lowers Aβ levels, according to several studies (Bao *et al.*, 2020). Apart from its potential to prevent the creation of harmful prefibrillar oligomers,

EGCG has also been proposed as a possible remodeler of preexisting amyloid fibrils. Since EGCG is unstable and oxidizes quickly to produce a range of products, most research is done at physiological pH (Sternke-Hoffmann *et al.*, 2020). Research has demonstrated that polyphenols can either stop Aβ oligomerization from happening or restructure and stabilize Aβ oligomers into forms that are safe. To produce unstructured Aβ oligomers, EGCG inhibits Aβ fibrillogenesis. Smaller, more amorphous, nontoxic protein aggregates are assembled from freshly formed oligomers with its assistance (El Gaamouch *et al.*, 2022). Catecholamine neurotransmitters have the ability to maintain Aβ in its oligomeric state, according to studies. Indeed, Aβ oligomer stabilization may involve the cooperation of NE and DA. An elevated oligomer concentration is indicated by the aggregated Aβ, which is significantly blurred when NE and DA are present (Allnutt & Matera, 2023).

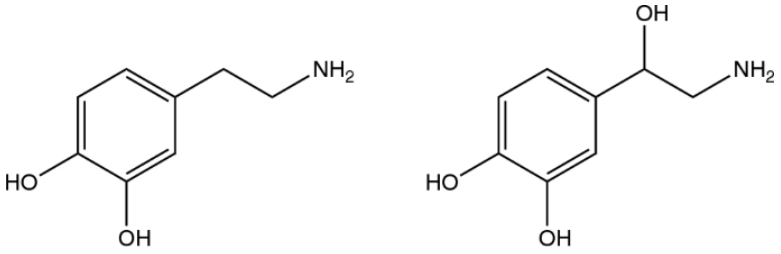



**Figure 6:** Structures of neurotransmitters examined for stabilization of Aβ oligomers.
*Source: Adopted from (Allnutt & Matera, 2023)*

An antioxidant, anti-inflammatory, and anticancer polyphenolic compound is curcumin. Its low bioavailability restricts efficacy despite its possible advantages in Alzheimer's disease (AD) models (Momma *et al.*, 2023). Enhancing bioavailability and brain translocation, GT863, a derivative of curcumin, was synthesized. Together with dual stabilization of Aβ and tau aggregation, in vivo studies showed that GT863 could ameliorate cognitive impairment in an AD mouse model. It would seem from this that GT863 is a good candidate for more study in the treatment of AD.

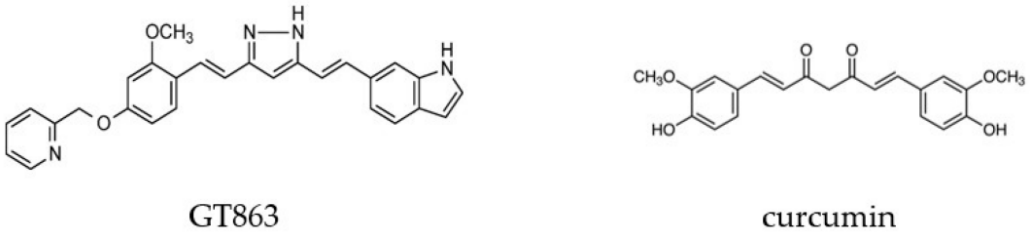



**Figure 7:** Structures of GT863 and curcumin.
*Source: Adopted from ref (Zhou et al., 2022)*

Few compounds that can disassemble pre-formed oligomers have progressed to the point of clinical trials, despite the fact that a large number of Aβ aggregation inhibitors have been discovered in vitro. Trimiprosate, also known as 3-amino-1-propanesulfonic acid; AlzhemedTM), has been shown to bind preferentially to pre-fibrillar (monomeric and oligomeric) forms of Antibody, thereby preventing their conversion into higher-order oligomers and fibrils (Ono & Tsuji, 2020). Moreover, metal ions control Aβ polymorphism, stability, and aggregation. Based on our simulations, the stabilizing effect is dependent on the size of the fibrillar oligomer and the type of alkali ion. Studies looked at how fibrillar Aβ oligomers of different sizes were affected by the three alkali metal ions Li+, Na+, and K+ (Huraskin & Horn, 2019). According to recent research, small molecules with anti-oxidative properties, the majority of which come from natural sources, can lessen the neurotoxicity of AβOs (Araki & Kametani, 2022). Aβ42 aggregates are more toxic than the more prevalent Aβ40 because Aβ42 peptides can form three-stranded motifs, which enable them to assemble into poreforming aggregates (ring- or barrel-shaped), and the brain environment—specifically, the presence of fatty acids—enhances the formation of these aggregates. We discover that lauric acid stabilizes these aggregates (Khatua *et al.*, 2021).

**Degradation of Amyloid-β Oligomers**

The degradation of Aβ in the brains of AD patients is a crucial area of study to help understand the underlying mechanism of Aβ degradation and to shed light on the disease's pathogenesis (Zhang *et al.*, 2020). Degrading the levels of accumulated Aβ aggregates and inhibiting Aβ aggregation are therefore important, and doing so has become essential for the potential application as an appealing therapeutic and preventive strategy for the treatment of AD (Cheng *et al.*, 2020). Furthermore, there are still few ways to assess the degree of Aβ degradation.

Circular dichroism (CD) and the thioflavin-T (ThT) fluorescence assay are frequently used to look into how the β-sheet structure in Aβ aggregates is being destroyed (Gao *et al.*, 2022). By tracking the decrease in Aβ concentration over time, the Aβ degradation has also been identified using sandwich enzyme-linked immunosorbent assay (ELISA) and western blot techniques (Rostami *et al.*, 2021). These methods do, however, still have a number of drawbacks, including a high potential for false positive/negative results or results that are subject to subjectivity, the need for careful handling and accuracy at every stage, and high individual costs associated with the preparation of antibodies and culture media. To measure the enzymatic breakdown of Aβ, some peptide mapping investigations are carried out, which involve gathering fractions from liquid chromatography (LC) and then using off-line mass spectrometry (MS) (Moracci *et al.*, 2021). Studies conducted recently indicate that nattokinase (NK) may play a part in the treatment of diseases related to Aβ42 aggregates, like AD, as it can gradually break down Aβ42 aggregates at neutral pH and body temperature (Chen *et al.*, 2018). After then, Aβ is eliminated by non-proteolytic or enzyme-mediated mechanisms. There are currently about 20 different proteases known as Aβ degrading enzymes (ADEs), which mediate the proteolytic degradation of Aβ (Sikanyika *et al.*, 2019). Aβ clearance can be categorized into two main groups: enzymatic and non-enzymatic. Enzymatic clearance involves the action of Aβ-degrading enzymes (ADEs), which function as proteases to break down Aβ peptides into smaller, less harmful forms. While most degradation is believed to occur within the brain, clearance may also happen in other areas where Aβ is found after being cleared from the brain. A variety of ADEs have been found from different classes of proteases, including metallo-serine, aspartyl, cysteine, and threonine proteases (see Table 1). Many of these proteases have the ability to break down multiple peptide substrates in various tissue locations (Żukowska *et al.*, 2023). Neprilysin (NEP) and insulin-degrading enzyme (IDE) are the most well-characterized AβDPs. They are both zinc-metalloendopeptidases that are primarily involved in the breakdown of monomeric species, though neprilysin has also been reported to hydrolyze Aβ oligomers (de Dios *et al.*, 2019). Insulin-degrading enzyme (IDE) is a widely distributed Zn2+-metalloprotease present in various human tissues and organs. Extensive research has suggested a strong link between IDE and Alzheimer's disease (AD). Clinical and in vivo investigations have consistently shown that reduced IDE levels in the brain of AD patients contribute to the advancement of the disease (Abramov-Harpaz & Miller, 2022). Enzymes such as endothelinconverting enzyme, neprilysin (NEP), insulin-degrading enzyme (IDE), and matrix metalloproteinase9 show a decrease in the accumulation of Aβ. While matrix metalloproteinase-9 enzyme was discovered to degrade both soluble Aβ species and Abfibers, IDE and NEP are reported to be able to remove soluble Aβ (Sahoo *et al.*, 2021). Zinc metalloproteases known as endothelin-converting enzymes, or ECEs, are made by astrocytes, endothelial cells, and neurons. ECE-1 and ECE-2 exhibit 59% homology and comparable catalytic activities; however, these activities differ in terms of their ideal pH, with ECE-1 activity requiring a physiological pH and ECE-2 activity requiring an acidic pH (5.5). They were proposed to be involved in the breakdown of monomeric Aβ before its secretion, and they mainly break down intracellular Aβ (Loeffler, 2023). One important protease that breaks down fibrin in blood clots is called plismin (Plm). Plm, along with tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), is one of the three components of plasmin-based thrombolysis (Yang *et al.*, 2020). Plm is derived from its inactive form, plasminogen (Plg). Amyloid-beta (Aβ) has been shown to be directly degraded by Plm, which also targets its monomeric and fibrillar forms while lessening their toxicity. This implies that Plm may have a part in resolving Aβ-related problems (Loeffler, 2023).

**Table 1:** Presents a list of enzymes that have shown the ability to degrade Aβ in laboratory studies. However, the complete characterization of each protein's biological significance is still incomplete. Neprilysin-2 (NEP-2) is referred to by various names in the literature, including SEP, NL1, MMEL1, and NE_PLP.

| **Aβ degrading enzymes** | **Aβ degrading enzymes** |
|---|---|
| Neprilysin (NEP) | Matrix metalloprotease-14 (MMP-14) |
| Endothelin-converting enzyme-1 (ECE-1) | Myelin basic protein (MBP) |
| Endothelin-converting enzyme-2 (ECE-2) | Plasmin |
| Angiotensin-1 converting enzyme (ACE) | Aminopeptidase A |
| Angiotensin converting enzyme-2 (ACE-2) | Mitochondrial presequence protease (PreP) |
| Insulin-degrading enzyme (IDE) | Acyl peptide hydrolase (APEH) |
| Matrix metalloproteinase-2 (MMP-2) | Cathepsin B |
| Matrix metalloproteinase-9 (MMP-9) | Cathepsin D |
| Beta secretase 1 (BACE 1) | Beta secretase 2 (BACE 2) |
| 26S proteasome. | |

*Source: Adopted from (Żukowska et al., 2023)*

## CONCLUSION

It is concluded that Amyloid-beta (Aβ) oligomers have important role in Alzheimer's disease (AD) pathogenesis, neuroinflammation and cognitive decline through liquid-liquid phase separation (LLPS) and dynamic aggregation. This study highlighted progress in targeting Aβ oligomers with metal complexes, small molecules and immunotherapies, which make stable nontoxic forms and control aggregation, or regulate degradation. Main challenges include the heterogeneity in structure and the desire for blood-brain barrier-permeable therapeutics. Innovative strategies, such as Aβ-degrading enzymes and LLPS inhibitors, offer breakthrough pathways for early intervention. Future studies should prefer in vivo validation for phase-separation modulators, microstructural characterization of oligomers and biomarkers for early detection. By combining chemical biology and neurotherapeutics, this field proceeds closer to disease-modifying treatments that degrade Aβ toxicity at its point source, offering hope for overstaying AD progression.

## REFERENCES


Abelein, A. (2023). Metal Binding of Alzheimer's Amyloid-β and Its Effect on Peptide Self-Assembly. *Accounts of Chemical Research, 56*(19), 2653-2663. https://doi.org/10.1021/acs.accounts.3c00370

Abramov-Harpaz, K., & Miller, Y. (2022). Insights into Non-Proteolytic Inhibitory Mechanisms of Polymorphic Early-Stage Amyloid β Oligomers by Insulin Degrading Enzyme. *Biomolecules, 12*(12). https://doi.org/10.3390/biom12121886

Alberti, S., & Hyman, A. A. (2021). Biomolecular condensates at the nexus of cellular stress, protein aggregation disease and ageing. *Nature Reviews Molecular Cell Biology, 22*(3), 196-213. https://doi.org/10.1038/s41580-020-00326-6

Allnutt, M. A., & Matera, K. M. (2023). Stabilization and Reduced Cytotoxicity of Amyloid Beta Aggregates in the Presence of Catechol Neurotransmitters. *Neurochemical Research, 49*(2), 379-387. https://doi.org/10.1007/s11064-023-04036-1

Amano, A., Sanjo, N., Araki, W., Anraku, Y., Nakakido, M., Matsubara, E., Tomiyama, T., Nagata, T., Tsumoto, K., Kataoka, K., & Yokota, T. (2023). Peripheral administration of nanomicelle-encapsulated anti-Aβ oligomer fragment antibody reduces various toxic Aβ species in the brain. *Journal of Nanobiotechnology, 21*(1). https://doi.org/10.1186/s12951-023-01772-y

Amzallag, E., & Hornstein, E. (2022). Crosstalk between Biomolecular Condensates and Proteostasis. *Cells, 11*(15). https://doi.org/10.3390/cells11152415

An, J., Kim, K., Lim, H. J., Kim, H. Y., Shin, J., Park, I., Cho, I., Kim, H. Y., Kim, S., McLean, C., Choi, K. Y., Kim, Y., Lee, K. H., & Kim, J. S. (2024). Early onset diagnosis in Alzheimer's disease patients via amyloid-β oligomers-sensing probe in cerebrospinal fluid. *Nature Communications, 15*(1). https://doi.org/10.1038/s41467-024-44818-x

Andrade, S., Ramalho, M. J., Loureiro, J. A., & Pereira, M. d. C. (2019). Natural Compounds for Alzheimer's Disease Therapy: A Systematic Review of Preclinical and Clinical Studies. *International Journal of Molecular Sciences, 20*(9). https://doi.org/10.3390/ijms20092313

Araki, W. (2023). Aβ Oligomer Toxicity-Reducing Therapy for the Prevention of Alzheimer's Disease: Importance of the Nrf2 and PPARγ Pathways. *Cells, 12*(10). https://doi.org/10.3390/cells12101386

Araki, W., & Kametani, F. (2022). Protection against Amyloid-β Oligomer Neurotoxicity by Small Molecules with Antioxidative Properties: Potential for the Prevention of Alzheimer's Disease Dementia. *Antioxidants, 11*(1). https://doi.org/10.3390/antiox11010132

Bao, J., Liu, W., Zhou, H.-y., Gui, Y.-r., Yang, Y.-h., Wu, M.-j., Xiao, Y.-f., Shang, J.-t., Long, G.-f., & Shu, X.-j. (2020). Epigallocatechin-3-gallate Alleviates Cognitive Deficits in APP/PS1 Mice. *Current Medical Science, 40*(1), 18-27. https://doi.org/10.1007/s11596-020-2142-z

Cascella, R., Bigi, A., Riffert, D. G., Gagliani, M. C., Ermini, E., Moretti, M., Cortese, K., Cecchi, C., & Chiti, F. (2022). A quantitative biology approach correlates neuronal toxicity with the largest inclusions of TDP-43. *Science Advances, 8*(30). https://doi.org/10.1126/sciadv.abm6376

Chen, H., McGowan, E. M., Ren, N., Lal, S., Nassif, N., Shad-Kaneez, F., Qu, X., & Lin, Y. (2018). Nattokinase: A Promising Alternative in Prevention and Treatment of Cardiovascular Diseases. *Biomarker Insights, 13*. https://doi.org/10.1177/1177271918785130

Cheng, Y., Tian, D.-Y., & Wang, Y.-J. (2020). Peripheral clearance of brain-derived Aβ in Alzheimer's disease: pathophysiology and therapeutic perspectives. *Translational Neurodegeneration, 9*(1). https://doi.org/10.1186/s40035-020-00195-1

Cline, E. N., Bicca, M. A., Viola, K. L., Klein, W. L., Perry, G., Avila, J., Moreira, P. I., Sorensen, A. A., & Tabaton, M. (2018). The Amyloid-β Oligomer Hypothesis: Beginning of the Third Decade. *Journal of Alzheimer's Disease, 64*(s1), S567-S610. https://doi.org/10.3233/jad-179941

de Dios, C., Bartolessis, I., Roca-Agujetas, V., Barbero-Camps, E., Mari, M., Morales, A., & Colell, A. (2019). Oxidative inactivation of amyloid beta-degrading proteases by cholesterol-enhanced mitochondrial stress. *Redox Biology, 26*. https://doi.org/10.1016/j.redox.2019.101283

Derreumaux, P., Nguyen, P., & Sterpone, F. (2022). https://doi.org/10.22541/au.167108799.96485165/v1

Diociaiuti, M., Bonanni, R., Cariati, I., Frank, C., & D'Arcangelo, G. (2021). Amyloid Prefibrillar Oligomers: The Surprising Commonalities in Their Structure and Activity. *International Journal of Molecular Sciences, 22*(12). https://doi.org/10.3390/ijms22126435

Du, H., Song, J., Ma, F., Gao, H., Zhao, X., Mao, R., He, X., & Yan, Y. (2023). Novel harmine derivatives as potent acetylcholinesterase and amyloid beta aggregation dual inhibitors for management of Alzheimer's disease. *Journal of Enzyme Inhibition and Medicinal Chemistry, 38*(1). https://doi.org/10.1080/14756366.2023.2281893

El Gaamouch, F., Chen, F., Ho, L., Lin, H.-Y., Yuan, C., Wong, J., & Wang, J. (2022). Benefits of dietary polyphenols in Alzheimer's disease. *Frontiers in Aging Neuroscience, 14*. https://doi.org/10.3389/fnagi.2022.1019942

Fish, P. V., Steadman, D., Bayle, E. D., & Whiting, P. (2019). New approaches for the treatment of Alzheimer's disease. *Bioorganic & Medicinal Chemistry Letters, 29*(2), 125-133. https://doi.org/10.1016/j.bmcl.2018.11.034

Foley, A. R., Lee, H.-W., & Raskatov, J. A. (2019). A Focused Chiral Mutant Library of the Amyloid β 42 Central Electrostatic Cluster as a Tool To Stabilize Aggregation Intermediates. *The Journal of Organic Chemistry, 85*(3), 1385-1391. https://doi.org/10.1021/acs.joc.9b02312

French, R. L., Grese, Z. R., Aligireddy, H., Dhavale, D. D., Reeb, A. N., Kedia, N., Kotzbauer, P. T., Bieschke, J., & Ayala, Y. M. (2019). Detection of TAR DNA-binding protein 43 (TDP-43) oligomers as initial intermediate species during aggregate formation. *Journal of Biological Chemistry, 294*(17), 6696-6709. https://doi.org/10.1074/jbc.RA118.005889

Gao, G., Zhang, T., Zhang, W., Luo, Z., Zhang, Z., Gu, Z., Yu, L., Mu, Q., & Sun, T. (2022). High efficiency and related mechanism of Au(RC) nanoclusters on disaggregating Aβ fibrils. *Journal of Colloid and Interface Science, 621,* 67-76. https://doi.org/10.1016/j.jcis.2022.04.085

Grasso, G., & Danani, A. (2020). Molecular simulations of amyloid beta assemblies. *Advances in Physics: X, 5*(1). https://doi.org/10.1080/23746149.2020.1770627

Haerianardakani, S., Kreutzer, A. G., Salveson, P. J., Samdin, T. D., Guaglianone, G. E., & Nowick, J. S. (2020). Phenylalanine Mutation to Cyclohexylalanine Facilitates Triangular Trimer Formation by β-Hairpins Derived from Aβ. *Journal of the American Chemical Society, 142*(49), 20708-20716. https://doi.org/10.1021/jacs.0c09281

Han, Y.-L., Yin, H.-H., Li, C., Du, J., He, Y., & Guan, Y.-X. (2025). Discovery of New Pentapeptide Inhibitors Against Amyloid-β Aggregation Using Word2Vec and Molecular Simulation. *ACS Chemical Neuroscience, 16*(6), 1055-1065. https://doi.org/10.1021/acschemneuro.4c00661

Hardenberg, M., Horvath, A., Ambrus, V., Fuxreiter, M., & Vendruscolo, M. (2020). Widespread occurrence of the droplet state of proteins in the human proteome. *Proceedings of the National Academy of Sciences, 117*(52), 33254-33262. https://doi.org/10.1073/pnas.2007670117

Hector, A., & Brouillette, J. (2021). Hyperactivity Induced by Soluble Amyloid-β Oligomers in the Early Stages of Alzheimer's Disease. *Frontiers in Molecular Neuroscience, 13*. https://doi.org/10.3389/fnmol.2020.600084

Huang, Y.-r., & Liu, R.-t. (2020). The Toxicity and Polymorphism of β-Amyloid Oligomers. *International Journal of Molecular Sciences, 21*(12). https://doi.org/10.3390/ijms21124477

Hughes, M. P., Sawaya, M. R., Boyer, D. R., Goldschmidt, L., Rodriguez, J. A., Cascio, D., Chong, L., Gonen, T., & Eisenberg, D. S. (2018). Atomic structures of low-complexity protein segments reveal kinked β sheets that assemble networks. *Science, 359*(6376), 698-701. https://doi.org/10.1126/science.aan6398

Huraskin, D., & Horn, A. H. C. (2019). Alkali ion influence on structure and stability of fibrillar amyloid-β oligomers. *Journal of Molecular Modeling, 25*(2). https://doi.org/10.1007/s00894-018-3920-4

Hwang, S. S., Chan, H., Sorci, M., Van Deventer, J., Wittrup, D., Belfort, G., & Walt, D. (2019). Detection of amyloid β oligomers toward early diagnosis of Alzheimer's disease. *Analytical Biochemistry, 566,* 40-45. https://doi.org/10.1016/j.ab.2018.09.011

Jang, C., Portugal Barron, D., Duo, L., Ma, C., Seabaugh, H., & Guo, Z. (2023). EPR Studies of Aβ42 Oligomers Indicate a Parallel In-Register β-Sheet Structure. *ACS Chemical Neuroscience, 15*(1), 86-97. https://doi.org/10.1021/acschemneuro.3c00364

Jehangir, M., Ali, R., Hui, W. X., & Wang, Y. (2024). An Updated Review of Amyloid Beta Oligomer Toxicity Inhibition and Detection for Alzheimer's Disease Diagnosis. *Cognizance Journal of Multidisciplinary Studies, 4*(7), 164-186. https://doi.org/10.47760/cognizance.2024.v04i07.015

Kanaan, N. M., Hamel, C., Grabinski, T., & Combs, B. (2020). Liquid-liquid phase separation induces pathogenic tau conformations in vitro. *Nature Communications, 11*(1). https://doi.org/10.1038/s41467-020-16580-3

Khatua, P., Jana, A. K., & Hansmann, U. H. E. (2021). Effect of Lauric Acid on the Stability of Aβ42 Oligomers. *ACS Omega, 6*(8), 5795-5804. https://doi.org/10.1021/acsomega.0c06211

König, A. S., Rösener, N. S., Gremer, L., Tusche, M., Flender, D., Reinartz, E., Hoyer, W., Neudecker, P., Willbold, D., & Heise, H. (2021). Structural details of amyloid β oligomers in complex with human prion protein as revealed by solid-state MAS NMR spectroscopy. *Journal of Biological Chemistry, 296*. https://doi.org/10.1016/j.jbc.2021.100499

Kubo, K., Watanabe, H., Kumeta, H., Aizawa, T., Seki, C., Nakano, H., Tokuraku, K., & Uwai, K. (2022). Chemical analysis of amyloid β aggregation inhibitors derived from Geranium thunbergii. *Bioorganic & Medicinal Chemistry, 68*. https://doi.org/10.1016/j.bmc.2022.116840

Kumar, R., Das, S., Mohite, G. M., Rout, S. K., Halder, S., Jha, N. N., Ray, S., Mehra, S., Agarwal, V., & Maji, S.

K. (2018). Cytotoxic Oligomers and Fibrils Trapped in a Gel-like State of α-Synuclein Assemblies. *Angewandte Chemie International Edition, 57*(19), 5262-5266. https://doi.org/10.1002/anie.201711854

Li, C. H., Coffey, E. L., Dall'Agnese, A., Hannett, N. M., Tang, X., Henninger, J. E., Platt, J. M., Oksuz, O., Zamudio, A. V., Afeyan, L. K., Schuijers, J., Liu, X. S., Markoulaki, S., Lungjangwa, T., LeRoy, G., Svoboda, D. S., Wogram, E., Lee, T. I., Jaenisch, R., & Young, R. A. (2020). MeCP2 links heterochromatin condensates and neurodevelopmental disease. *Nature, 586*(7829), 440-444. https://doi.org/10.1038/s41586-020-2574-4

Li, J., Liao, W., Huang, D., Ou, M., Chen, T., Wang, X., Zhao, R., Zhang, L., Mei, L., Liu, J., & Luan, P. (2023). Current strategies of detecting Aβ species and inhibiting Aβ aggregation: Status and prospects. *Coordination Chemistry Reviews, 495*. https://doi.org/10.1016/j.ccr.2023.215375

Limbocker, R., Chia, S., Ruggeri, F. S., Perni, M., Cascella, R., Heller, G. T., Meisl, G., Mannini, B., Habchi, J., Michaels, T. C. T., Challa, P. K., Ahn, M., Casford, S. T., Fernando, N., Xu, C. K., Kloss, N. D., Cohen, S. I. A., Kumita, J. R., Cecchi, C., Zasloff, M., Linse, S., Knowles, T. P. J., Chiti, F., Vendruscolo, M., & Dobson, C. M. (2019). Trodusquemine enhances Aβ42 aggregation but suppresses its toxicity by displacing oligomers from cell membranes. *Nature Communications, 10*(1). https://doi.org/10.1038/s41467-018-07699-5

Liu, H., Zhao, X., Chen, J., Win, Y. Y., & Cai, J. (2025). Unnatural foldamers as inhibitors of Aβ aggregation via stabilizing the Aβ helix. *Chemical Communications, 61*(24), 4586-4594. https://doi.org/10.1039/d4cc05280c

Loeffler, D. A. (2023). Experimental approaches for altering the expression of Abeta-degrading enzymes. *Journal of Neurochemistry, 164*(6), 725-763. https://doi.org/10.1111/jnc.15762

Luo, F., Gui, X., Zhou, H., Gu, J., Li, Y., Liu, X., Zhao, M., Li, D., Li, X., & Liu, C. (2018). Atomic structures of FUS LC domain segments reveal bases for reversible amyloid fibril formation. *Nature Structural & Molecular Biology, 25*(4), 341-346. https://doi.org/10.1038/s41594-018-0050-8

Madhu, P., & Mukhopadhyay, S. (2021). Distinct types of amyloid-β oligomers displaying diverse neurotoxicity mechanisms in Alzheimer's disease. *Journal of Cellular Biochemistry, 122*(11), 1594-1608. https://doi.org/10.1002/jcb.30141

Mantile, F., & Prisco, A. (2020). Vaccination against β-Amyloid as a Strategy for the Prevention of Alzheimer's Disease. *Biology, 9*(12). https://doi.org/10.3390/biology9120425

Martinez Pomier, K., Ahmed, R., & Melacini, G. (2020). Catechins as Tools to Understand the Molecular Basis of Neurodegeneration. *Molecules, 25*(16). https://doi.org/10.3390/molecules25163571

Matsushima, Y., Irie, Y., Kageyama, Y., Bellier, J. P., Tooyama, I., Maki, T., Kume, T., Yanagita, R. C., & Irie, K. (2022). Structure Optimization of the Toxic Conformation Model of Amyloid β42 by Intramolecular Disulfide Bond Formation. *ChemBioChem, 23*(8). https://doi.org/10.1002/cbic.202200029

Matuszyk, M. M., Garwood, C. J., Ferraiuolo, L., Simpson, J. E., Staniforth, R. A., & Wharton, S. B. (2021). Biological and methodological complexities of beta-amyloid peptide: Implications for Alzheimer's disease research. *Journal of Neurochemistry, 160*(4), 434-453. https://doi.org/10.1111/jnc.15538

Mohammed, A. A., Barale, S. S., Kamble, S. A., Paymal, S. B., & Sonawane, K. D. (2023). Molecular insights into the inhibition of early stages of Aβ peptide aggregation and destabilization of Alzheimer's Aβ protofibril by dipeptide D-Trp-Aib: A molecular modelling approach. *International Journal of Biological Macromolecules, 242*. https://doi.org/10.1016/j.ijbiomac.2023.124880

Mokra, D., Joskova, M., & Mokry, J. (2022). Therapeutic Effects of Green Tea Polyphenol (−)-Epigallocatechin-3-Gallate (EGCG) in Relation to Molecular Pathways Controlling Inflammation, Oxidative Stress, and Apoptosis. *International Journal of Molecular Sciences, 24*(1). https://doi.org/10.3390/ijms24010340

Momma, Y., Tsuji, M., Oguchi, T., Ohashi, H., Nohara, T., Ito, N., Yamamoto, K., Nagata, M., Kimura, A. M., Nakamura, S., Kiuchi, Y., & Ono, K. (2023). The Curcumin Derivative GT863 Protects Cell Membranes in Cytotoxicity by Aβ Oligomers. *International Journal of Molecular Sciences, 24*(4). https://doi.org/10.3390/ijms24043089

Moracci, L., Crotti, S., Traldi, P., Agostini, M., Cosma, C., & Lapolla, A. (2021). Role of mass spectrometry in the study of interactions between amylin and metal ions. *Mass Spectrometry Reviews, 42*(3), 984-1007. https://doi.org/10.1002/mas.21732

Mroczko, B., Groblewska, M., Litman-Zawadzka, A., Kornhuber, J., & Lewczuk, P. (2017). Amyloid β oligomers (AβOs) in Alzheimer's disease. *Journal of Neural Transmission, 125*(2), 177-191. https://doi.org/10.1007/s00702-017-1820-x

Muhammad, J., Xiaohui, W., Kashif, k., Umar, A., & Ke, Z. (2024). Chemical regulation of Tau oligomers in phase separation in Alzheimer's disease. *World Journal of Biology Pharmacy and Health Sciences, 19*(2), 380-390. https://doi.org/10.30574/wjbphs.2024.19.2.0534

Muhammad, J., Xiaohui, W., Ye, Z., Umar, A., Kashif, k., & Wang, c. (2024). Inhibition of amyloid beta oligomer, fibrils, and peptide using nanoparticles to disrupt Alzheimer's pathogenesis. *World Journal of Advanced Research and Reviews, 23*(2), 343-357. https://doi.org/10.30574/wjarr.2024.23.2.2349

Ono, K., & Tsuji, M. (2020). Protofibrils of Amyloid-β are Important Targets of a Disease-Modifying Approach for Alzheimer's Disease. *International Journal*

*of Molecular Sciences, 21*(3). https://doi.org/10.3390/ijms21030952

Pagano, K., Tomaselli, S., Molinari, H., & Ragona, L. (2020). Natural Compounds as Inhibitors of Aβ Peptide Aggregation: Chemical Requirements and Molecular Mechanisms. *Frontiers in Neuroscience, 14*. https://doi.org/10.3389/fnins.2020.619667

Panza, F., Dibello, V., Sardone, R., Zupo, R., Castellana, F., Leccisotti, I., Moretti, M. C., Altamura, M., Bellomo, A., Daniele, A., Solfrizzi, V., Resta, E., & Lozupone, M. (2025). Successes and failures: the latest advances in the clinical development of amyloid–β–targeting monoclonal antibodies for treating Alzheimer's disease. *Expert Opinion on Biological Therapy, 25*(3), 275-283. https://doi.org/10.1080/14712598.2025.2463963

Peng, C., Wang, X., Li, Y., Li, H.-W., & Wong, M. S. (2019). Versatile fluorescent probes for near-infrared imaging of amyloid-β species in Alzheimer's disease mouse model. *Journal of Materials Chemistry B, 7*(12), 1986-1995. https://doi.org/10.1039/c9tb00161a

Penke, B., Szűcs, M., & Bogár, F. (2020). Oligomerization and Conformational Change Turn Monomeric β-Amyloid and Tau Proteins Toxic: Their Role in Alzheimer's Pathogenesis. *Molecules, 25*(7). https://doi.org/10.3390/molecules25071659

Phan, H. T. T., Samarat, K., Takamura, Y., Azo-Oussou, A. F., Nakazono, Y., & Vestergaard, M. d. C. (2019). Polyphenols Modulate Alzheimer's Amyloid Beta Aggregation in a Structure-Dependent Manner. *Nutrients, 11*(4). https://doi.org/10.3390/nu11040756

Rana, M., & Sharma, A. K. (2019). Cu and Zn interactions with Aβ peptides: consequence of coordination on aggregation and formation of neurotoxic soluble Aβ oligomers. *Metallomics, 11*(1), 64-84. https://doi.org/10.1039/c8mt00203g

Rostami, J., Mothes, T., Kolahdouzan, M., Eriksson, O., Moslem, M., Bergström, J., Ingelsson, M., O'Callaghan, P., Healy, L. M., Falk, A., & Erlandsson, A. (2021). Crosstalk between astrocytes and microglia results in increased degradation of α-synuclein and amyloid-β aggregates. *Journal of Neuroinflammation, 18*(1). https://doi.org/10.1186/s12974-021-02158-3

Russ, H., Mazzanti, M., Parsons, C., Riemann, K., Gebauer, A., & Rammes, G. (2022). The Small Molecule GAL-201 Efficiently Detoxifies Soluble Amyloid β Oligomers: New Approach towards Oral Disease-Modifying Treatment of Alzheimer's Disease. *International Journal of Molecular Sciences, 23*(10). https://doi.org/10.3390/ijms23105794

Saha, D., & Jana, B. (2022). Identifying the Template for Oligomer to Fibril Conversion for Amyloid-β (1-42) Oligomers using Hamiltonian Replica Exchange Molecular Dynamics. *ChemPhysChem, 23*(24). https://doi.org/10.1002/cphc.202200393

Sahoo, B. R., Panda, P. K., Liang, W., Tang, W.-J., Ahuja, R., & Ramamoorthy, A. (2021). Degradation of Alzheimer's Amyloid-β by a Catalytically Inactive Insulin-Degrading Enzyme. *Journal of Molecular Biology, 433*(13). https://doi.org/10.1016/j.jmb.2021.166993

Savastano, A., Flores, D., Kadavath, H., Biernat, J., Mandelkow, E., & Zweckstetter, M. (2020). Disease-Associated Tau Phosphorylation Hinders Tubulin Assembly within Tau Condensates. Angewandte Chemie International *Edition, 60*(2), 726-730. https://doi.org/10.1002/anie.202011157

Sehar, U., Rawat, P., Reddy, A. P., Kopel, J., & Reddy, P. H. (2022). Amyloid Beta in Aging and Alzheimer's Disease. *International Journal of Molecular Sciences, 23*(21). https://doi.org/10.3390/ijms232112924

Senapati, S., Secchi, V., Cova, F., Richman, M., Villa, I., Yehuda, R., Shenberger, Y., Campione, M., Rahimipour, S., & Monguzzi, A. (2023). Noninvasive Treatment of Alzheimer's Disease with Scintillating Nanotubes. *Advanced Healthcare Materials, 12*(32). https://doi.org/10.1002/adhm.202301527

Sharari, S., Vaikath, N. N., Tsakou, M., Ghanem, S. S., & Vekrellis, K. (2023). Screening for Novel Inhibitors of Amyloid Beta Aggregation and Toxicity as Potential Drugs for Alzheimer's Disease. *International Journal of Molecular Sciences, 24*(14). https://doi.org/10.3390/ijms241411326

Shin, Y., Berry, J., Pannucci, N., Haataja, M. P., Toettcher, J. E., & Brangwynne, C. P. (2017). Spatiotemporal Control of Intracellular Phase Transitions Using Light-Activated optoDroplets. *Cell, 168*(1-2), 159-171.e114. https://doi.org/10.1016/j.cell.2016.11.054

Sikanyika, N. L., Parkington, H. C., Smith, A. I., & Kuruppu, S. (2019). Powering Amyloid Beta Degrading Enzymes: A Possible Therapy for Alzheimer's Disease. *Neurochemical Research, 44*(6), 1289-1296. https://doi.org/10.1007/s11064-019-02756-x

Song, C., Shi, J., Zhang, P., Zhang, Y., Xu, J., Zhao, L., Zhang, R., Wang, H., & Chen, H. (2022). Immunotherapy for Alzheimer's disease: targeting β-amyloid and beyond. *Translational Neurodegeneration, 11*(1). https://doi.org/10.1186/s40035-022-00292-3

Stanković, I. M., Niu, S., Hall, M. B., & Zarić, S. D. (2020). Role of aromatic amino acids in amyloid self-assembly. *International Journal of Biological Macromolecules, 156,* 949-959. https://doi.org/10.1016/j.ijbiomac.2020.03.064

Sternke-Hoffmann, R., Peduzzo, A., Bolakhrif, N., Haas, R., & Buell, A. K. (2020). The Aggregation Conditions Define Whether EGCG is an Inhibitor or Enhancer of α-Synuclein Amyloid Fibril Formation. *International Journal of Molecular Sciences, 21*(6). https://doi.org/10.3390/ijms21061995

Taylor, A. I. P., & Staniforth, R. A. (2022). General Principles Underpinning Amyloid Structure. *Frontiers in Neuroscience, 16*. https://doi.org/10.3389/fnins.2022.878869

Thapliyal, S., Singh, T., Handu, S., Bisht, M., Kumari, P., Arya, P., Srivastava, P., & Gandham, R. (2021). A Review on Potential Footprints of Ferulic Acid for

Treatment of Neurological Disorders. *Neurochemical Research, 46*(5), 1043-1057. https://doi.org/10.1007/s11064-021-03257-6

Tzioras, M., McGeachan, R. I., Durrant, C. S., & Spires-Jones, T. L. (2022). Synaptic degeneration in Alzheimer disease. *Nature Reviews Neurology, 19*(1), 19-38. https://doi.org/10.1038/s41582-022-00749-z

Uddin, M. S., Al Mamun, A., Kabir, M. T., Ashraf, G. M., Bin-Jumah, M. N., & Abdel-Daim, M. M. (2020). Multi-Target Drug Candidates for Multifactorial Alzheimer's Disease: AChE and NMDAR as Molecular Targets. *Molecular Neurobiology, 58*(1), 281-303. https://doi.org/10.1007/s12035-020-02116-9

Viola, K. L., & Klein, W. L. (2015). Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis. *Acta Neuropathologica, 129*(2), 183-206. https://doi.org/10.1007/s00401-015-1386-3

Volynsky, P. E., Urban, A. S., Pavlov, K. V., Bershatsky, Y. V., Bocharova, O. V., Kryuchkova, A. K., Zlobina, V. V., Gavrilenkova, A. A., Dolotova, S. M., Kamynina, A. V., Zangieva, O. T., Taldaev, A., Batishchev, O. V., Okhrimenko, I. S., Rakitina, T. V., Efremov, R. G., & Bocharov, E. V. (2025). Diverse Interactions of Sterols with Amyloid Precursor Protein Transmembrane Domain Can Shift Distribution Between Alternative Amyloid-β Production Cascades in Manner Dependent on Local Lipid Environment. *International Journal of Molecular Sciences, 26*(2). https://doi.org/10.3390/ijms26020553

Wang, C., Wang, X., Chan, H. N., Liu, G., Wang, Z., Li, H. W., & Wong, M. S. (2020). Amyloid-β Oligomer-Targeted Gadolinium-Based NIR/MR Dual-Modal Theranostic Nanoprobe for Alzheimer's Disease. *Advanced Functional Materials, 30*(16). https://doi.org/10.1002/adfm.201909529

Wegmann, S., Eftekharzadeh, B., Tepper, K., Zoltowska, K. M., Bennett, R. E., Dujardin, S., Laskowski, P. R., MacKenzie, D., Kamath, T., Commins, C., Vanderburg, C., Roe, A. D., Fan, Z., Molliex, A. M., Hernandez-Vega, A., Muller, D., Hyman, A. A., Mandelkow, E., Taylor, J. P., & Hyman, B. T. (2018). Tau protein liquid–liquid phase separation can initiate tau aggregation. *The EMBO Journal, 37*(7). https://doi.org/10.15252/embj.201798049

Wu, Y., Guo, S., Wang, K., & Kang, J. (2023). The interaction of peptide inhibitors and Aβ protein: Binding mode analysis, inhibition of the formation of Aβ aggregates, and then exert neuroprotective effects. *Frontiers in Aging Neuroscience, 15*. https://doi.org/10.3389/fnagi.2023.1139418

Yang, D., Zhu, W., Wang, Y., Tan, F., Ma, Z., Gao, J., & Lin, X. (2020). Selection of mutant μplasmin for amyloid-β cleavage in vivo. *Scientific Reports, 10*(1). https://doi.org/10.1038/s41598-020-69079-8

Zbinden, A., Pérez-Berlanga, M., De Rossi, P., & Polymenidou, M. (2020). Phase Separation and Neurodegenerative Diseases: A Disturbance in the Force. *Developmental Cell, 55*(1), 45-68. https://doi.org/10.1016/j.devcel.2020.09.014

Zeng, M., Shang, Y., Araki, Y., Guo, T., Huganir, R. L., & Zhang, M. (2016). Phase Transition in Postsynaptic Densities Underlies Formation of Synaptic Complexes and Synaptic Plasticity. *Cell, 166*(5), 1163-1175.e1112. https://doi.org/10.1016/j.cell.2016.07.008

Žerovnik, E., & Venko, K. (2023). Protein Condensates and Protein Aggregates: In Vitro, in the Cell, and In Silico. *Frontiers in Bioscience-Landmark, 28*(8). https://doi.org/10.31083/j.fbl2808183

Zhang, W., Gao, G., Ma, Z., Luo, Z., He, M., & Sun, T. (2020). Au23(CR)14 nanocluster restores fibril Aβ's unfolded state with abolished cytotoxicity and dissolves endogenous Aβ plaques. *National Science Review, 7*(4), 763-774. https://doi.org/10.1093/nsr/nwz215

Zhou, X., Venigalla, M., Raju, R., & Münch, G. (2022). Pharmacological considerations for treating neuroinflammation with curcumin in Alzheimer's disease. *Journal of Neural Transmission, 129*(5-6), 755-771. https://doi.org/10.1007/s00702-022-02480-x

Żukowska, J., Moss, S. J., Subramanian, V., & Acharya, K. R. (2023). Molecular basis of selective amyloid-β degrading enzymes in Alzheimer's disease. *The FEBS Journal, 291*(14), 2999-3029. https://doi.org/10.1111/febs.16939