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Review

The Pharmacology and Dual Role of Proteostasis in Amyloidoses

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Abstract

Cellular protein quality control comprises the ubiquitin proteasome system, autophagy, and molecular chaperones, which maintain proteostasis in healthy tissues. The failure of these cellular and molecular pathways, which normally safeguard the proteome, can cause and even exacerbate amyloidoses, the abnormal accumulation of proteins into amyloid fibrils that drive neurodegeneration. Amyloidoses can also damage peripheral organs; examples include light chain amyloidosis, cardiac amyloidosis, and renal amyloidosis. Restoring proteostasis and preventing protein aggregation is therefore an active area of research, with several promising strategies under investigation. Among these approaches, small-molecule modulators that restore proteostasis are attractive candidates because they may simultaneously rescue multiple quality control mechanisms and remodel aggregates to improve their accessibility to endogenous degradation pathways. Here, we propose that amyloid pathology disrupts multiple proteostasis pathways simultaneously, creating a feed-forward cascade in which the breakdown of interconnected proteostasis networks drives progressive protein aggregation, which in turn propels proteostasis collapse. Pharmacological interventions targeting protein aggregation offer opportunity to rescue interconnected proteostasis networks, which could, in turn, cooperatively manage or eliminate pathogenic amyloid burden.

Keywords: proteostasis; amyloidosis; ubiquitin–proteasome system; autophagy; molecular chaperones; neurodegeneration

1. Introduction

Proteinopathies are a diverse group of diseases characterized by the aggregation and accumulation of proteins, both intracellularly and extracellularly, resulting in cellular dysfunction and tissue damage. At its core, amyloidoses involve the breakdown of proteostasis, an extensive network of cellular and molecular pathways responsible for maintaining protein quality control and facilitating degradation. Dysfunction in several known proteostasis pathways contributes to aggregation, not only by failing to eliminate misfolded proteins, but also by actively potentiating the formation of proteotoxic oligomeric fragments that catalyze prionogenic template-based seeding [1–6]. Indeed, several amyloidogenic proteins, including Aβ, tau, α-synuclein, polyQ-Htt, and TDP-43, can propagate through prion-like mechanisms in which misfolded aggregates seed the conversion of native proteins and spread pathology between cells [7]. This propagation adds complexity to therapeutic intervention, as strategies that enhance proteostasis may influence both intracellular aggregate clearance and the generation or release of seeding-competent species. Although numerous

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reviews have examined individual proteostasis pathways, the coordinated interactions between the ubiquitin–proteasome system, autophagy, and molecular chaperones, as well as their implications for therapeutic intervention, remain less clearly synthesized. This review integrates these mechanisms and examines how their collective dysfunction contributes to amyloid pathology, while highlighting strategies to restore proteostasis through coordinated modulation of multiple pathways, including small molecules that act directly on fibrils and those targeting macromolecular chaperones and protein degradation pathways.

Prion diseases, including Creutzfeldt–Jakob disease (CJD), kuru, fatal familial insomnia (FFI), and Gerstmann–Sträussler–Scheinker syndrome (GSS), involve the abnormal aggregation of prion protein (PrP) and were among the first identified amyloidoses [8–10]. Among neurodegenerative diseases, hallmark proteinopathies also include Alzheimer's disease (AD), characterized by amyloid-beta (Aβ) and tau aggregates, and tauopathies such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and chronic traumatic encephalopathy (CTE), which are marked by tau aggregation [11–17]. Other neurodegenerative conditions, like Parkinson's disease (PD), multiple system atrophy (MSA), and Lewy body dementia (LBD), are amyloidoses involving alpha-synuclein (α-syn) aggregates, while Huntington's disease (HD) results from polyglutamine expansions in the huntingtin protein (Htt), leading to aggregation [18–21]. Additionally, aggregates of superoxide dismutase 1 (SOD1), TDP-43, or FUS proteins have been linked to neurodegeneration in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [22–25].

The structure, aggregation propensity, and cellular processing of amyloidogenic proteins can be influenced by post-translational modifications (PTMs), including phosphorylation, acetylation, truncation, glycosylation, and ubiquitination. While not the focus of this review (see Moon et al. for extensive discussion of PTMs in amyloid disease), we briefly discuss recent key examples of PTMs and their impact on chaperone binding to amyloids [26]. In particular, phosphorylation of α-syn at serine-129 alters the conformational dynamics of its C-terminal region and enhances recruitment of the co-chaperone DNAJB1 to fibrils, suggesting that specific modifications may regulate chaperone recognition and influence disaggregation efficiency [27]. Structural studies further demonstrate that PTMs can reshape amyloid fibril architecture. For example, cryo-electron microscopy analyses of light-chain amyloid fibrils containing modifications such as pyroglutamylation, N-glycosylation, and disulfide bonding have revealed fibril conformations that differ from previously described non-modified fibrils, highlighting that chemical modifications can influence both fibril polymorphism, and their recognition by cellular clearance mechanisms [28]. Similarly, structural studies of phosphorylated tau variants have shown that specific phosphorylation patterns can produce distinct fibril core architectures, indicating that combinations of PTMs could influence aggregate structures and the proteostasis pathways they interact with [29].

2. Systemic and Organ-Specific Amyloidoses

Although a preponderance of amyloidoses involve neurodegeneration, several systemic amyloidoses damage peripheral organs, leading to proteinopathies and death. Among them are light chain amyloidosis, also known as AL amyloidosis, caused by aggregation of immunoglobulin light chain deposits, and AA amyloidosis, a rare occurrence resulting from serum amyloid A protein aggregation associated with chronic inflammatory conditions [30–33]. Organ-specific amyloidoses include islet amyloid polypeptide (IAPP) aggregation in pancreatic beta cells, which is implicated in type 2 diabetes, and renal amyloidoses, such as ALECT2, caused by LECT2 amyloid deposits in the kidney [34,35]. Cardiac amyloidoses are largely characterized by transthyretin (TTR) amyloidosis, which can manifest from both wild-type and variant TTR. Wild-type ATTR, also known as senile

systemic amyloidosis (SSA), is marked by TTR deposits in elderly hearts, while variant TTR characterizes familial ATTR amyloidosis and results from a hereditary gene variant. TTR fibrils also accumulate in other tissues, including the kidney, and brain, leading to systemic and neurologic dysfunctions [36–38].

Together, neurological and systemic proteinopathies can compromise the livelihood of people in nearly any walk of life, often leading to fatal disease. Despite the diversity in protein composition and structure, these disorders share common pathological mechanisms centered on protein misfolding and aggregation, underscoring the potential opportunity to treat disease using therapeutic strategies that work hand-in-hand to eliminate aggregate burden, both to restore and leverage proteostasis machinery.

3. Proteostasis in Health and Neurodegeneration

In healthy tissues, proteostasis is maintained via the ubiquitin–proteasome system (UPS), chaperones, lysosomes, and micro- and macro-autophagy [39]. However, with proteotoxic stress and aging, proteins fail to be regulated through these quality control systems and aggregate into amyloid fibrils and plaques [40]. In fact, the accumulation of amyloids in neurodegenerative diseases such as AD, PD, and HD is associated with dysfunctional protein quality control in the brain (Figure 1). For example, in AD, key components of these pathways are impaired, causing dysfunction of protein homeostasis and even higher tau and Aβ aggregation [41]. It has been shown that protein homeostasis is impaired in PD as well, and that failure of these mechanisms leads to further α-syn aggregation [42]. Likewise, in HD, the UPS, chaperones, and autophagy machineries are impaired [43].

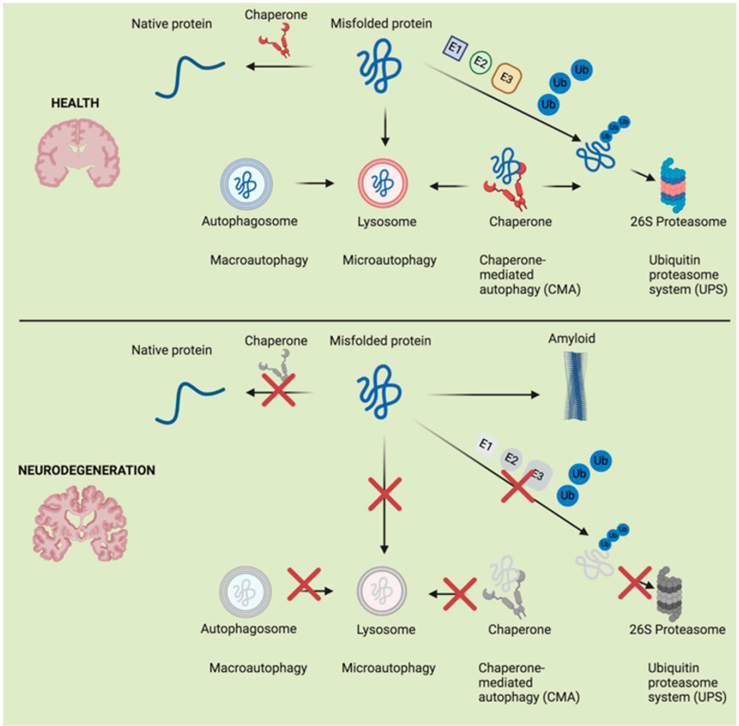


Figure 1. Protein quality control in health and disease. In a healthy brain protein homeostasis is controlled by several systems such as macroautophagy, microautophagy, chaperone-mediated autophagy (CMA), chaperone proteins, and ubiquitin proteasome system (UPS). These systems ensure that when a protein begins to misfold, it is either degraded or restored to its native form. However, in neurodegenerative conditions, one or more of these systems become impaired, leading to the formation of amyloids. Created in BioRender. Albanese, A. (2026). BioRender.com/m45l742.

4. Roles for the Proteasomes in Neurodegeneration

The ubiquitin proteasome system (UPS) is one of the two main proteolytic systems necessary for protein quality control. This pathway breaks down toxic substrates, such as intrinsically disordered, misfolded, and oxidatively damaged proteins, into small peptides [44–46]. In ubiquitin-dependent proteolysis, damaged proteins are tagged with polyubiquitin by a series of enzymes (E1, E2, E3) and directed to the proteasome. The proteasome consists of a 20S catalytic core (CP) and a 19S regulatory particle (RP), which acts as a proteasome activator. When these two components combine, they form the 26S proteasome [47]. Once a protein is tagged with ubiquitin, Rpn10 and Rpn13, proteasomal ubiquitin receptors situated in the 19S RP, recognize the polyubiquitin chain on the targeted protein and recruit it for degradation. The ubiquitin tag is removed by deubiquitinases Rpn11, USP14, and UCH37 in concert with the ATPase activity of the regulatory particle, which unfolds and pulls the protein into the 20S catalytic chamber for degradation into oligopeptides ranging from 3 to 15 amino acids [47–50]. When substrates such as misfolded, oxidatively damaged, or intrinsically disordered proteins (IDPs) such as tau and Aβ accumulate, they are degraded directly by the 20S proteasome. The 20S proteasome interacts directly with these substrates, shifting from a closed-gate to an open-gate conformation, allowing the target protein to be degraded. Regulatory particles such as PA28 and PA200 can also induce the open-gate conformation and facilitate the degradation process [46].

Proteasome activity is decreased in several neurodegenerative diseases [51,52], exacerbating and potentially even causing protein aggregation. Specifically, AD brains show significantly decreased proteasomal activity and that proteasome deficiency can disproportionately affect specific brain regions, such as the hippocampus and straight gyrus, which are also the regions most prone to AD pathology [53,54]. In sporadic PD, proteasomal subunits are reduced in dopaminergic neurons of the substantia nigra pars compacta (SNc), which is one of the regions of the brain most affected by PD, but not in other brain regions unaffected by PD, such as the cerebellum [55,56]. Likewise, in HD, the most significant proteasome activity loss occurs in the striatum region of the brain, which is the most affected region of the brain in this disease [57,58]. Proteasome activity is also impaired and decreased in systemic and organ-specific amyloidosis. For example, in TTR amyloidoses, including TTR cardiac amyloidosis and TTR-related familial amyloidosis polyneuropathy (TTR-FAP) characterized, respectively, by TTR aggregates built up in the heart and in peripheral nerves, proteasome activity is reduced [59,60]. Similarly, Casas et al. showed decreased proteasome activity in protein extract from human pancreatic islets after incubation with human islet amyloid polypeptide (hIAPP) [61].

However, whether region-specific proteasome dysfunction acts as a primary trigger of aggregation or instead arises as a consequence of accumulating misfolded proteins remains unresolved. Impaired proteasome function has been proposed both as a causative factor and as a downstream consequence in the pathogenesis of neurodegenerative diseases [52]. When proteasomal capacity becomes insufficient, misfolded proteins can accumulate and promote aggregate formation. Conversely, aggregated proteins themselves directly inhibit proteasome function, further compromising ubiquitin–proteasome system activity and establishing a pathogenic feed-forward cycle [62,63].

One of the mechanisms of proteasome inhibition is through a physical interaction between amyloids such as Aβ 1–42, α-syn, and huntingtin exon 1 with a polyQ-expansion (Htt-53Q) and the 19S regulatory particle of the 26S proteasome, thereby interfering with 19S-mediated gate opening of the 20S core, impairing the proteasome and preventing substrates from entering the proteasomal proteolytic chamber [52–54]. In addition, both Aβ42 and tau fibrils have been found to inhibit proteasome activity to an extent comparable to classical proteasome inhibitors [53–66]. Likewise, α-syn inhibits the 20S and 26S protea-

some, only when in an aggregated, but not monomeric, form [67]. Notably, filamentous Htt fibrils extracted from inclusion bodies (IBs) inhibit the activity of the 26S proteasome, but not of the 20S core, through interaction with the 19S regulatory caps [68]. Importantly, proteasome impairment has been observed not only in reductionist in vitro systems but also in human AD brain tissue and transgenic mouse models, where pathological tau and Aβ species have been shown to associate with proteasome subunits and correlate with reduced proteasomal activity [53,65,66]. While these findings support the in vivo relevance of amyloid–proteasome interactions, the precise quantitative contribution of direct proteasome inhibition within the complex cellular environment of the diseased brain remains to be fully defined. Another line of evidence suggesting that the UPS is impaired in AD, is that ubiquitination is associated with neurofibrillary tangles and senile plaques as well as having a variant, UBB+1, which prevents ubiquitin-dependent proteolysis [69–71]. Notably, UBB+1 is also associated with other tauopathies such as PSP and Pick's disease, as well as polyglutamine diseases such as HD, but does not pertain to synucleinopathies such as PD, LBD, and MSA [72,73]. This indicates that reduced proteasomal activity is a common marker that is associated with protein pathology, and its restoration might help clear pathogenic proteins, offering potential therapeutic benefits for the disease.

5. Drugs Targeting Proteasome Pathways

Several studies on proteasome enhancers have been conducted in the context of neurodegeneration. Several phenothiazines such as trifluprom azine (EC_{50} = 7.8 μM), thioridazine (EC_{50} = 12 μM), metixene (EC_{50} = 11.9 μM) and clomipramine (EC_{50} = 12.4 μM), and the neuroleptic agent chlorpromazine (EC_{50} = 14.8 μM) have been identified as proteasome enhancers. The latter induced degradation of α-syn and tau in vitro assays [74]. The potential of phenothiazines as proteasome activators is also supported by a study by Medina et al., where Aβ levels were reduced in an AD mouse model upon administration of methylene blue, which is a chlorpromazine analog [75]. Similarly, AM-404 and MK-886, small molecules assessed by Trader et al., behaved as 20S proteasome enhancers (EC_{50} = 32 μM) and were able to enhance α-syn degradation in cell culture [76]. Additionally, natural products such as betulinic acid, ursolic acid, and oleuropein, have been classified as stimulators or gate-openers, which promote substrate entry in the 20S proteasome catalytic chamber by enhancing proteasomal substrate binding or gate-opening [46]. However, a critical limitation of proteasome activation strategies is selectivity. Because the proteasome regulates turnover of numerous short-lived regulatory proteins involved in cell cycle control, signaling, and stress responses, global enhancement of proteasomal activity may risk accelerating degradation of essential substrates and perturbing cellular homeostasis [77]. Some studies suggest that certain 20S proteasome activators preferentially enhance degradation of intrinsically disordered or oxidatively damaged proteins, which are characteristic of many aggregation-prone species, potentially conferring a degree of substrate bias [78,79]. Nevertheless, whether sufficient selectivity can be achieved in vivo without disrupting tightly regulated proteostasis networks remains an important open question.

While the above proteasome enhancers have been studied in the context of neurodegeneration, proteasome inhibitors have also been explored and emerged as potential therapeutic candidates for AL amyloidosis. Inhibiting proteasome activity induces apoptosis of plasma cells responsible for producing amyloid light chains, therefore representing a possible therapeutic strategy. Proteasome inhibitors candidates include bortezomib, carfilzomib and ixazomib, although further studies are necessary and ongoing to minimize toxicity effects in vivo [80,81]. For example, carfilzomib, an irreversible proteasome inhibitor, has been associated with an increased incidence of cardiovascular toxicity, including heart failure and acute coronary syndromes [80]. Because patients with AL amyloidosis

frequently present with multisystem organ involvement, they are especially susceptible to treatment-related toxicities, necessitating careful regimen selection that balances therapeutic efficacy with safety and tolerability [82]. Moving forward, consolidated effort centered on the development and validation of strategies and molecules that prevent and/or destabilize protein aggregates may provide a targeted route for therapeutic intervention. Further elucidating the molecular and biochemical mechanisms underlying therapy-associated cardiovascular injury remains an important area of future investigation.

Another therapeutic strategy for combating amyloidoses is through the use of proteolysis-targeting chimeras (PROTACs). These bifunctional molecules consist of a target-binding ligand, which specifically binds to the aggregation-prone protein, and an E3 ligase ligand, which recruits an E3 ubiquitin ligase. This ligase tags the target protein for degradation via the UPS. PROTACs have been developed and studied for a range of target proteins, including tau, α-syn, TDP-43, and variant Htt [83]. For example, the hetero-bifunctional QC-01-175 binds to tau in neuronal cell models of FTD and enhances its ubiquitination and subsequent proteasomal degradation [84]. Several other PROTACs are being synthesized against tau. In 2016, PROTAC TH006 was the first one to target and induce degradation of soluble tau in Neuro-2a cells, SH-SY5Y cells, and 3xTg-AD mouse models [85]. Another tau-targeting PROTAC worth mentioning is PROTAC C004019, which stimulated elimination of soluble tau in HEK293, SH-SY5Y cells, and in 3xTg-AD mouse models, and also reduced Aβ-induced neurotoxicity [86]. In 2020, six PROTAC designs were patented, featuring specific α-syn-binding motifs like benzothiazole derivatives and linked to CRBN or VHL E3 ligases. A Patent Highlight published in ACS Medicinal Chemistry Letters describes the chemical structures and biological activity for determined using ELISA and activity in HEK293 α-syn A53T biosensor cells, presenting categorical data for several PROTACs that achieved over 65% α-syn degradation [87]. However, PROTAC activity depends on productive ternary complex formation between the target and the recruited E3 ligase, and degradation efficiency is influenced by intracellular concentration and cooperativity. At high concentrations, unproductive binary complexes may predominate (the "hook effect"), potentially limiting catalytic efficiency [88,89]. The 'hook effect' can occur due at high concentrations, resulting in a bell-shaped dose–response curve, when excess PROTAC binds target proteins and E3 ligases separately creating binary complexes, rather than productive ternary complexes that promote proteasome-mediated degradation. More recently, PROTACs based on an inhibitor of α-syn aggregation (sery384) have demonstrated effective α-syn aggregate degradation in vitro, with the most potent compound reducing aggregates in a dose- and time-dependent manner, alleviating toxicity [87,90]. Recently, Tseng et al. developed a PROTAC named JMF4560 that effectively decreased TDP-43 aggregates in neuronal cells, as well as improving motility in transgenic *C. elegans* [91]. PROTACs targeting Htt have also been developed by companies such as Arvinas and Origami Therapeutics, which are able to selectively degrade variant Htt, without affecting the wild-type protein [83].

The application of PROTACs in neurodegenerative diseases faces ongoing translational challenges, including limited blood–brain barrier permeability and brain distribution due to their sometimes relatively large and complex structures. In addition, reliance on broadly expressed E3 ligases such as CRBN and VHL may restrict regional specificity [92,93]. Furthermore, a fundamental biophysical limitation arises from the aggregated state of target proteins, in which key epitopes are buried within tightly packed fibril cores, reducing ligand accessibility and rendering these species poorly druggable [94]. Despite these challenges, recent studies have shown hopeful progress and efforts are ongoing to optimize the pharmacokinetic and pharmacodynamic properties of PROTACs, as well as improving blood–brain barrier penetration [95]. These considerations underscore the need for careful

pharmacokinetic optimization and safety evaluation when translating PROTAC-based strategies to neurodegenerative disorders.

6. Autophagy–Lysosomal System in Neurodegeneration

The autophagy–lysosomal system is the other main proteolytic system for protein homeostasis. While the UPS degrades mostly short-lived proteins, autophagy is responsible for the regulation of long-lived proteins and organelles [96]. Autophagy is categorized into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [97]. Microautophagy involves direct engulfment of degradative organelles by lysosomes, while CMA selectively targets specific proteins, which are recognized by chaperones and transported into lysosomes. Macroautophagy uses autophagosomes to enclose and deliver larger structures like damaged organelles to lysosomes for degradation, especially under stress conditions [98]. The endolysosomal system is another essential cellular pathway for degradation and recycling of proteins, lipids, and other cellular components through their internalization into endosomes, followed by degradation after endosomes fuse with lysosomes [99].

Numerous studies have shown that autophagy is impaired in AD, and a lack of clearance of Aβ and tau promotes their accumulation and exacerbates neurodegeneration. For example, autophagosomes form but fail to fuse with lysosomes for degradation, causing a build-up of waste in the brain of AD patients [100,101]. Consistent with this, the accumulation of autophagosomes observed in AD is generally attributed to impaired autophagic flux and defective clearance or maturation steps rather than solely to increased autophagy initiation, suggesting that therapeutic intervention should target the later steps in the autophagy pathway [102]. Another issue that results in autophagy dysfunction is the decrease in lysosomal activity, which can be caused by AD-related genes and environmental risk factors such as ApoE and amyloid precursor protein (APP) or by presenilin 1 (PS1) variants, that disrupts lysosome acidification, thereby impairing autophagic degradation [103]. However, more recent studies suggest that lysosomal proteolytic defects in AD may not solely depend on major changes in lysosomal pH and may instead involve altered lysosomal calcium homeostasis or compensatory mechanisms that partially preserve hydrolase activity [104,105]. This indicates that lysosomal impairment in AD is mechanistically complex and remains an area of active investigation. Finally, it has been shown that, in AD, increased levels of acetylated tau directly impairs CMA by preventing translocation to the lysosome, leading to a vicious cycle of CMA failure and tau accumulation [106]. Furthermore, other checkpoints in the endolysosomal pathway are also impaired in AD. Accumulation of tau halts endosomal sorting complex transport-III (ESCRT-III) from forming, which is essential for autophagosome–lysosome formation, and tau aggregates also induce lysosomal abnormalities in mice [64]. In addition, depletion or dysfunction of ESCRT components enhances endolysosomal membrane damage, facilitating the cytosolic escape and prion-like propagation of tau seeds, further exacerbating aggregate spread and neuronal vulnerability [107]. Together, these findings indicate that autophagy impairment in AD likely occurs at multiple stages of the pathway rather than arising from a single primary defect. The accumulation of tau and Aβ impairs the autophagy–lysosomal pathway, which in turn leads to higher accumulation of these aggregates, creating a vicious cycle. It has been suggested that restoring autophagy is a therapeutic strategy to reduce the accumulation of tau aggregates [101,103,106].

In PD, α-syn overexpression impairs macroautophagy, and the PD-associated W437X variant of PTEN-induced putative kinase 1 (PINK1), is unable to promote autophagy, as its interaction with the key autophagic regulator Beclin1 is compromised [108]. Furthermore, the common PD common variant form of the leucine-rich repeat kinase 2 (LRRK2) is rarely

degraded by CMA, unlike what occurs under normal conditions [109]. In addition, α-syn fibrils have been shown to sequester and promote degradation of ESCRT-III components, thereby compromising endolysosomal membrane integrity and facilitating further propagation of aggregation [110]. Structural analyses of ESCRT-III assembly further highlight the mechanistic complexity of its membrane remodeling activity, supporting a dynamic and regulated model of endolysosomal dysfunction in neurodegeneration [111].

In HD, autophagic dysfunction is still not fully understood. While autophagy has been shown to favor the degradation of soluble and insoluble Htt, autophagy impairment has been observed in several HD models [109,112,113]. Dysfunctions in the system comprise inefficient macroautophagy with autophagic vacuoles not being able to recognize cytosolic cargo and reduced beclin 1 function, which is essential for autophagosome formation [109,114,115]. Growing evidence indicates that Htt is also degraded by CMA.

CMA activity increases in response to macroautophagy dysfunction; but this compensatory CMA activity gradually declines with aging, resulting in the emergence of pathological symptoms [116]. Systemic amyloidoses are often associated with impaired autophagic clearance. In conditions such as AL amyloid cardiomyopathy, immunoglobulin light chain proteins exacerbate this impairment, further enhancing amyloid accumulation and increasing cardiac toxicity [117]. Likewise, in type 2 diabetes, increased amounts of hIAPP oligomers induce defective autophagy in rats [118].

Moreover, a plethora of studies indicate that reduced autophagy, as well as reduced proteasome activity, are hallmarks of aging [119,120]. Since AD, PD and HD are aging-associated neurodegenerative diseases, understanding these aging mechanisms can reveal new insights into disease pathogenesis and potential therapeutic targets. For example, restoring autophagy has resulted in extended lifespan and alleviated age-associated diseases in animal models [121]. Likewise, enhancing basal autophagy has been found to ameliorate PD and HD neurodegenerative pathology in animal models [109,122].

7. Therapeutic Strategies Targeting Autophagy–Lysosomal Pathways

Targeting autophagy is an emerging approach for treating amyloidoses. It has been shown that Aβ accumulation leads to an increase in mammalian target of rapamycin (mTOR) signaling, which modulates autophagy. Pharmacological agents such as rapamycin, which promote autophagy by inhibiting mTOR signaling, have been successful in alleviating Aβ and tau pathology in AD animal models as well as in improving the viability of hIAPP-expressing cells [123,124]. However, mTOR is a central regulator of cellular growth, metabolism, and immune function [124], and chronic systemic inhibition has been associated with metabolic dysregulation, insulin resistance, and immunosuppression [125–127]. Accordingly, therapeutic strategies targeting mTOR require careful optimization of dosing, tissue specificity, and treatment duration to enhance autophagic clearance while minimizing systemic toxicity [128]. Beyond mTOR inhibition, additional small molecule enhancers (SMERs) have been widely investigated in neurodegenerative disease models. For instance, SMER10, SMER18, and SMER28 have been shown to promote autophagosome synthesis, facilitating the clearance of α-syn and variant Htt in mammalian cells. Additionally, these molecules demonstrated efficacy in a HD *Drosophila* model, where they enhanced the removal of toxic protein aggregates [129]. The disaccharide trehalose is another therapeutic target against proteinopathies, as it has been shown to reduce Aβ secretion in AD mouse models through both autophagy-dependent and independent mechanisms [130]. Recently, Kim et al. showed that MSL-7, an autophagy enhancer, decreases hIAPP oligomer aggregation and oligomer-induced apoptosis of β-cells in cellular models [131].

Autophagy-targeting chimera molecules (AUTACs) and autophagosome-tethering compounds (ATTECs) offer an innovative approach for enhancing protein degradation via

the autophagy pathway. These molecules are structured with three main components: a ligand that binds to the target protein, a linker to connect the ligands, and a degradation tag—typically a guanine derivative—that is crucial for recruiting the autophagic machinery (in the case of AUTACs) or a ligand that binds to the autophagosome protein LC3 (in ATTECs). This design facilitates the selective degradation of aggregated or misfolded proteins, offering therapeutic potential for amyloid-related diseases and other proteinopathies. For instance, Ji et al. have developed an AUTAC that mediates degradation of pathological tau in murine models [132]. ATC161 is a chimeric compound that targets α-syn aggregates for lysosomal degradation and results in reduced glial inflammation and improved locomotive activity in PD mice models [133]. Additionally, in 2019, Li et al. reported the first mHtt-LC3 linker compounds capable of facilitating variant Htt degradation via the lysosomal pathway in cultured primary cortical neurons, HD flies, and mouse brains [134]. However, several mechanistic and translational limitations remain. In AUTACs, the precise mechanism by which S-guanylation induces K63-linked polyubiquitination and promotes autophagic targeting is not yet fully understood, leaving key aspects of substrate recognition and selectivity unresolved [135,136]. Furthermore, the broader cellular consequences of guanine derivative–mediated tagging remain insufficiently characterized, raising concerns that unintended S-guanylation of endogenous proteins could potentially interfere with basal autophagic flux [137,138]. In the case of ATTECs, the structural determinants governing LC3 binding have not been fully defined, and challenges related to compound stability and efficient intracellular delivery represent significant barriers to clinical translation [139]. Moreover, because LC3 participates in multiple autophagic pathways, including non-selective bulk degradation, the degree to which true substrate specificity can be achieved without unintended off-target effects warrants further investigation [135,139]. Multiple studies have also been conducted regarding CMA-targeting molecules. In 2004, peptide-based molecules enhancing degradation of Aβ by CMA were designed, followed by bi-functional molecules targeting mHtt and α-syn, in 2010 and 2014, respectively [140–142]. Importantly, autophagy exhibits a context-dependent, dual role in cellular homeostasis. Under conditions of stress, moderate activation of autophagy can promote cell survival by removing damaged organelles and misfolded proteins, thereby limiting proteotoxic burden and preserving cellular function. However, sustained or excessive autophagic activity may overwhelm degradative capacity, leading to the accumulation of incompletely processed material or unintended degradation of essential cellular components [143]. This shift from protective to potentially deleterious effects underscores the complexity of therapeutically modulating autophagy. Therefore, therapeutic strategies must aim to enhance aggregate clearance without indiscriminately increasing global autophagic flux or disrupting basal housekeeping functions. A deeper understanding of the molecular determinants that govern this balance will be critical for designing interventions that maximize therapeutic benefit while minimizing unintended consequences.

8. Molecular Chaperones in Neurodegeneration

Molecular chaperones are proteins essential for maintaining cellular protein quality by assisting other proteins in folding, refolding, stabilization, and disaggregation. While chaperones differ in mechanism, they help preserve clients in active conformations and prevent misfolding and aggregation, especially under stress, by binding to unfolded or partially folded proteins for stabilization. Molecular chaperones are typically categorized as either foldases, which assist in protein folding in an ATP-dependent manner, or holdases, which prevent protein aggregation in an ATP-independent manner [144,145]. Several classes of chaperones exist in cells; among these, heat-shock proteins (Hsps) are upregulated when the amount of aggregation-prone folding proteins increases, especially in conditions of

stress [146]. The constitutively expressed Hsc70 and the stress-inducible Hsp70, specifically, play significant roles in binding misfolded proteins and either facilitating refolding or degradation through proteasomal or autophagic pathways. The activity of Hsp70 is dependent on ATP hydrolysis, which is regulated by chaperones of the HSP40 (also known as DnaJ) family and nucleotide-exchange factors [146,147].

Molecular chaperones are crucial for cellular homeostasis and are implicated in preventing diseases caused by protein misfolding, including neurodegenerative disorders like AD, PD, and HD [146,148–150]. Specifically, increasing Hsp70 levels reduces both tau and Aβ levels by binding to them and preventing self-aggregation as well as facilitating their degradation [151,152]. Additionally, Hsp70 and Hsp90 modulate APP metabolism and the folding of proteins associated with it, which is crucial since APP is a key protein in AD and its improper processing can lead to the formation of Aβ. Another chaperone significant in AD and related diseases is the AAA+ ATPase valosin-containing protein (VCP), which helps disaggregate amyloid-like tau fibrils in a proteasome-dependent manner. Furthermore, variants in VCP have been characterized for multiple neurodegenerative diseases including AD, PD, ALS, and FTD [153].

In HD, Hsp70, together with its cochaperone Hsp40, interferes with htt fibrillization in an ATP-dependent manner, limiting the formation of insoluble amyloid-like aggregates and promoting the accumulation of more soluble, less toxic species, consistent with a protective role against polyQ-induced neurodegeneration [154].

In PD, several Hsps (Hsp70, HspB1, HspB2, HspB3, HspB5, HspB6 and HspB8) and J-domain proteins (DNAJB1, DNAJB2, DNAJB6 and DNAJB8) prevent α-syn aggregation. Multiple HspB family members directly modulate α-syn assembly: HspB8 potently inhibits wild-type and mutant α-syn fibril formation, HSPB2/HSPB3 hetero-oligomers suppress aggregation, HspB1 (Hsp27) and HspB5 (αB-crystallin) inhibit oligomer and fibril formation primarily through transient chaperone–client interactions, and HspB6 acts as a lipid-dependent chaperone that prevents α-syn aggregation in the presence of lipid membranes, together supporting distinct yet complementary roles of HspB proteins in limiting α-syn aggregation [150,155–159]. Chaperones not only prevent early nucleation and halt fibril elongation, but are also able to disaggregate α-syn fibrils in PD and polyQ-containing Htt in HD via the action of Hsp70 disaggregase and DNAJB6 [144,160–162].

Under conditions of stress or aging, chaperone functionality can become impaired, resulting in the excessive accumulation of APP fragments and the formation of Aβ plaques [163]. In PD, co-chaperones such as CHIP and Parkin modulate Hsp70/Hsp90 complexes by directing client proteins toward either refolding or proteasomal degradation; dysregulation of this balance can contribute to neuronal dysfunction and protein aggregation [164]. Therefore, molecular chaperones are currently being targeted and studied as promising therapeutic strategies; potential treatments could focus on enhancing chaperone functions to reduce protein aggregation or improve cell protection against neurodegenerative stressors [163,164]. For example, it has been shown that injecting AD mice with recombinant human (rh) Bri2 BRICHOS chaperone domain decreases gliosis and deposition of Aβ plaques, highlighting the potential of chaperones to target amyloids [165,166]. Furthermore, myricetin, a polyphenolic flavonoid, has been found to increase Hsp70 levels as well as ubiquitin ligase levels in cells, reducing the aggregation of SOD1 variants in ALS and α-syn in PD [167].

It is important to note that chaperones interact with numerous essential client proteins and recognize exposed hydrophobic regions common to many partially folded or misfolded proteins, reflecting an inherent selective promiscuity rather than strict specificity for individual amyloids [168]. While increased Hsp70 levels can enhance proteostasis capacity and reduce amyloid accumulation, global modulation of these chaperones risks

perturbing normal proteostasis. This highlights the need for client- or complex-specific intervention. Accordingly, emerging therapeutic strategies aim to selectively modulate defined chaperone–cochaperone assemblies rather than broadly activate Hsp70; for example, the BAG2–Hsp70 complex directly targets tau and delivers it to the proteasome, and enhancing this interaction, rather than globally activating Hsp70, promotes selective clearance of misfolded tau while preserving essential chaperone functions [169]. In parallel, although the Hsp70–DNAJB1 disaggregation machinery can dismantle α-syn fibrils in vitro, its physiological relevance remains uncertain [170]. Disaggregation efficiency depends on fibril conformation and thermodynamic stability, and chaperone-mediated processing can generate seeding-competent species that promote further aggregation [171,172]. Moreover, under physiologically relevant concentrations of α-syn monomers, Hsp70-driven disaggregation is critically reduced and may even facilitate aggregation [173]. Together, these findings underscore that selective targeting of specific aggregation-prone species remains a significant mechanistic and therapeutic challenge that should be carefully considered in future research.

9. Cellular Proteostasis and Neurodegeneration: A Double-Edged Sword

Protein degradation plays a critical role in cellular health by eliminating damaged or misfolded proteins through pathways like the ubiquitin–proteasome system, molecular chaperones, and autophagy. However, aggregate elimination pathways function as a double-edged sword. On one hand, proper degradation helps prevent toxic protein aggregation; on the other, incomplete or dysregulated degradation can produce harmful intermediates or promote seeding of aggregates which can exacerbate disease pathology. Specifically, it has been shown that the proteasome breaks down fibrils into smaller aggregates, because it is unable to fully degrade the misfolded protein, leading to the accumulation of toxic and seeding-competent fragments in both AD and HD [174–176]. The bimodal activity of the UPS, which fragments aggregates in some contexts and eliminates them in others, suggests that proteasomal activity can be either beneficial or detrimental depending on the extent of aggregate elimination, potentially influencing disease progression. Similarly to UPS activity, chaperone activity can be seen as a double-edged sword. While they help manage and reduce toxic protein aggregates like Aβ, tau, and α-syn, chaperones can also inadvertently stabilize intermediate aggregates or contribute to the formation of smaller, seeding-competent fragments that propagate pathology [155]. For example, studies using human cells and primary mouse neurons have shown that through VCP activity tau fibrils are broken down in seeding-competent fragments in AD [177]. Notably, VCP engages distinct cofactors that influence seed replication efficiency, supporting a model in which cellular context determines whether VCP activity favors seed disassembly or further amplification [178]. In PD, despite α-syn disaggregation by chaperones being cytoprotective in vitro, other studies have shown the opposite effects in vivo and it is only by diminishing, rather than increasing, chaperone disaggregation activity that toxic α-syn aggregates are reduced in *C. elegans* [155].

Finally, abnormal autophagic activity is observed in neurodegenerative diseases such as AD, PD, HD and ALS, and whether autophagosomes are beneficial or detrimental to cells during disease is still unknown [115,179]. In fact, neuronal autophagy can also cause neuronal death due to oxidative stress and overexpression of the A53T variant α-syn, both pathogenic signatures of PD [115,180]. In HD, Htt aggregates activate the endosomal–lysosomal system, leading to autophagy-induced cell death, and in AD, autophagy can also cause production of Aβ [181].

The dual, bimodal effects of proteostatic machinery suggest that any given process involving protein disaggregation cannot be classified solely as protective or destructive.

Instead, the outcome of aggregate processing depends on mechanistic parameters such as the extent to which aggregates are decomposed (disaggregated) and through downstream proteolysis, and the capacity of cellular degradation pathways to eliminate intermediate species. Incomplete or partial disaggregation may generate proteotoxic, seeding-competent intermediates, whereas efficient and extensive degradation and full proteolytic clearance is more likely to eliminate harmful species, terminate seed amplification, and ensure successful removal of aggregates through pathways such as the UPS or autophagy–lysosomal system. Additional factors that might influence this balance include cofactor composition, aggregate conformation and thermodynamic stability, and the efficiency of downstream degradation pathways. These considerations highlight how the same proteostatic machinery can produce distinct outcomes depending on cellular context (Figure 2).

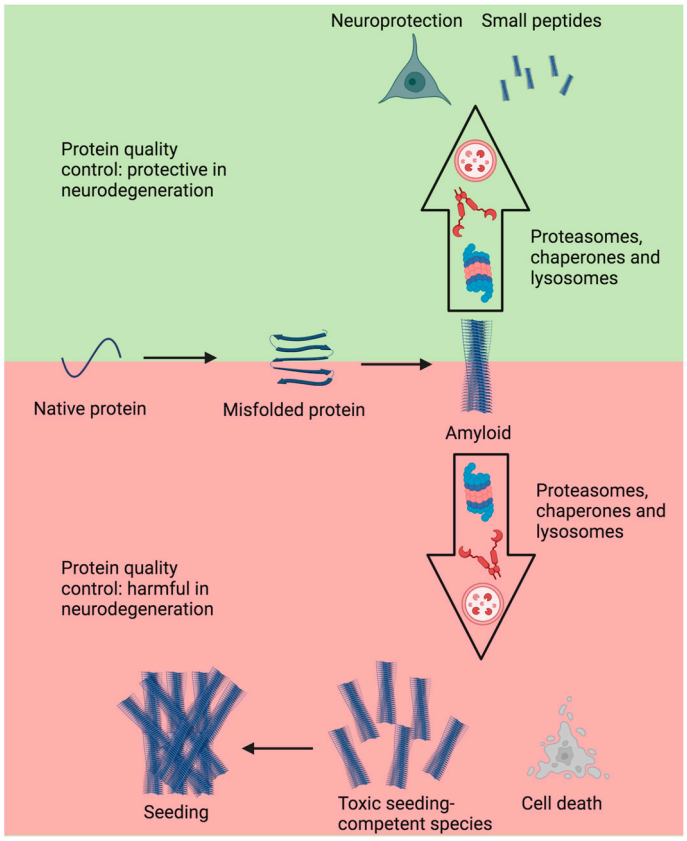


Figure 2. The bimodal role of proteostatic systems. Protein quality control systems could be both protective and destructive in neurodegeneration. On one hand they could prevent seeding by extensive disaggregation and complete proteolysis (Green). On the other hand, they could exacerbate seeding by incomplete or partial amyloid disaggregation, therefore generating more toxic, seeding-competent species (Red). Created in BioRender. Albanese, A. (2026). BioRender.com/q67a393.

10. Small Molecule Disaggregases of Amyloids and Protein Aggregates

We have thus far discussed therapeutic strategies for the treatment of amyloidoses that work via acting on components of the proteolytic systems. There are also a number of possible small molecules that act directly on amyloidogenic proteins via disaggregating or disrupting existing amyloids. Many of these small molecules, consisting mostly of natural products, have yet to be tested clinically but have been shown experimentally to exert an anti-amyloid effect. One class of these small molecule disaggregants are polyphenols, which are a family of natural products isolated from plant sources. Many polyphenols are pan-assay interference compounds (PAINS) and are known to potentially cause false positive experimental results [182–184]. Polyphenols also can aggregate into colloids, or

condensates, which can then increase their affinity for proteins enhancing their disaggregase power but also potentially generating non-specific interactions that may interfere with assay results [185–187]. As such, the activity of polyphenols has required careful biophysical validation in controlled systems, including direct visualization methods by electron microscopy (TEM or cryo-EM) or atomic force microscopy (AFM).

Natural product small-molecule disaggregants, including polyphenols, have provided important mechanistic insight into the disaggregation mechanism, offering novel insight into the therapeutic potential of small molecule disaggregases. Curcumin is a member of the polyphenol family and is naturally found in turmeric. Curcumin was found to be able to disaggregate Aβ, α-syn, and TTR fibrils, as well as tau oligomers, with reduced fibril count observed via TEM [188–193]. EGCG is another polyphenol and is naturally found in green tea. EGCG has also been shown to disaggregate preformed Aβ, α-syn, tau, and TTR fibrils, with AFM, TEM, or cryo-EM data validating these results [193–196]. More members of the polyphenol family have also demonstrated this anti-amyloid activity; namely, the polyphenols ginnalin A, myricetin, morin, quercetin, catechin, epicatechin, and kaempferol were shown to destabilize Aβ fibrils, with ginnalin A showing reduced fibril count via AFM, and myricetin via TEM [197,198]. The natural product DHM was found to disaggregate patient-derived AD tau fibrils, with a reduction in fibril count confirmed via TEM [199]. Collectively, these in vitro studies highlight the strong propensity of phenolic small molecules to disaggregate protein fibrils.

A number of natural product disaggregants outside of the polyphenols exist as well. The natural product brazilin originates from the *Caesalpinia sappan* plant, and has been shown to disassemble Aβ, α-syn, and IAPP fibrils, with reduced fibril count observed via TEM and AFM [200–202]. Tanshinone I and II are compounds isolated from *Salvia miltiorrhiza*, and have demonstrated Aβ and α-syn fibril disaggregation activity (results validated via AFM and TEM) [203,204]. In addition, phenolic neurotransmitters, including dopamine (and its precursor L-DOPA) and noradrenaline, were found to disaggregate AD tau fibrils to varying extents, demonstrating that endogenous brain small molecules also possess disaggregating activity [205].

Breakthrough biophysical studies investigating amyloid formation and disaggregation have led to the emergence of synthetic disaggregants with evidence of efficacy demonstrated through a ranging variety of biophysical and in vivo systems. CryoEM structures of the polyphenol, EGCG, bound to AD tau fibrils revealed an inhibitor/disaggregase binding site that was exploited for in silico drug discovery [196]. This effort led to the disclosure of several new synthetic, brain-permeable disaggregants with ranging efficacy measured for tau and other amyloids. Of these, CNS-11 displayed efficacy α-synuclein fibrils discovery [206]. Crucially, analogs of CNS-11 have been further refined leading to demonstrated efficacy in a transgenic tauopathy mouse model. Disaggregase treatment led to robust CNS permeability and reductions in AT8 hippocampal tau immunoreactivity and insoluble tau following 8-week treatment [207]. Furthermore, certain peptide-based tau inhibitors are now recognized as disaggregases with similar molecular effects to the small molecules described above [208]. Peptide-based disaggregases are proposed to fragment tau by a mechanism similar to small molecules, where inhibitor co-assembly nucleated by pathological protein fibrils creates mechanical strain causing, leading both fibril types to fracture. Cycles of co-assembly followed by fracture ultimately eliminates pathological fibrils. Effects seen in a transgenic tauopathy mouse model include improved memory function and reduced tau pathology.

While the studies described in detail above were validated using combinations of human pathological specimens and transgenic animal models, an important consideration regarding these disaggregants is that some aspects of the studies are necessarily conducted

using recombinant fibrils and transgenic animal lines that often display amyloid fibrils with conformations that differ from those found in patient samples [209,210]. At the moment, disaggregases appear to display a degree of pan-amyloid activity, which has rendered efficacy animal studies. The extent to which selectivity for specific amyloid folds can be targeted remains to be determined.

It should be noted that the anti-amyloid activity of many small molecules, particularly polyphenols, is often dependent on disaggregase concentration and aggregate load. Some compounds display bimodal behavior, where one concentration level may inhibit amyloid aggregation while another concentration level may have weaker effects or even promote aggregation. Additionally, potential therapeutics for CNS disorders need to be able to permeate the blood–brain barrier, which adds another limitation when considering which drugs might be effective in a clinical setting. As a result, aggregation inhibition observed in vitro does not always translate directly to activity in vivo, and additional attention to pharmacokinetics and steady state dose must be carefully considered for these potential drugs' viability as therapeutics [205,211].

One example which was also used as a foothold to research further disaggregants, is a cryo-EM structure of EGCG and AD tau fibrils. EGCG itself has very low blood–brain barrier permeability, but by using this structure as a basis, existing small molecule libraries with more favorable properties were docked in silico. Of the hits, the compounds CNS-11 and CNS-12 were shown to act as tau fibril disaggregants [196]. CNS-11 and its analog CNS-11g have also been shown to disaggregate α-syn fibrils derived from MSA [206]. Another example involves the natural product penicillic acid, which was found to inhibit tau aggregation in cell models and to reduce AD tau fibril count via TEM. Penicillic acid was predicted to have blood–brain barrier permeability, but was also flagged for potential mutagenicity. Using penicillic acid as a basis, a chemically similar analog was found that still effectively inhibited AD tau seeding in cell models while retaining predicted blood–brain barrier permeability and lacking the predicted mutagenicity. This specific example would require further experimentation to validate these predicted characteristics, but overall it shows promise in leveraging knowledge of existing natural product disaggregases as chemical probes to discover new small molecules with more favorable properties [212].

11. Small Molecule Inhibitors of Amyloidogenic Protein Aggregation

A number of small molecules exert an anti-amyloid effect via the inhibition of amyloidogenic protein aggregation, rather than by disaggregation of existing amyloids. Two examples that have reached the market are the small molecules tafamidis and the more recent acoramidis, which are two of the few available disease-modifying treatments for cardiac amyloidosis. Tafamidis and acoramidis both work as TTR aggregation inhibitors by stabilizing the tetrameric form of TTR, which prevents it from dissociating into monomer and forming amyloid deposits [213–215]. This works best when the disease is caught early before many existing amyloid deposits can be found, or when considering ATTR phenotypes where ATTR fibrils are composed only of monomers (Type B) [216,217]. Despite these limitations, tafamidis was a landmark achievement as the first FDA-approved drug to treat transthyretin amyloid cardiomyopathy. It also provided the first pharmacological evidence that protein aggregation directly causes tissue degeneration and disease.

A number of polyphenols show activity as inhibitors of amyloidogenic protein aggregation. Curcumin, previously mentioned as a disaggregant, is also able to inhibit Aβ, tau, α-syn, and TTR aggregation [188–193,218]. Another previously mentioned disaggregant, EGCG, was shown to inhibit the formation of Aβ, α-syn, tau, TTR, and variant Htt aggregates [193,219,220]. The polyphenols ginnalin A, myricetin, morin, quercetin, catechin, epicatechin, and kaempferol were shown to inhibit Aβ fibril formation alongside

their disaggregation activity [197,198]. The polyphenols baicalein, delphinidin, exifone, gallocatechin gallate, gossypetin, and theaflavine were all shown to inhibit the formation of Aβ, α-syn, and tau fibrils in vitro with IC_{50} values below 10 uM. Epigallocatechin, gallocatechin, myricetin, rosmarinic acid, and 2,3,4-trihydroxybenzophenone demonstrated the same effect towards all three fibril types but with IC_{50} values below 20 uM. Dopamine chloride, (+)-α-tocopherol, and procyanidin B2 were shown to inhibit only α-syn fibril formation (IC_{50} < 20 uM), while procyanidin B1 was shown to inhibit both Aβ and α-syn fibril formation (IC_{50} < 20 uM). Catechin gallate and luteolin were shown to inhibit only Aβ fibril formation (IC_{50} < 10 uM) [219].

Looking at other natural products outside of the polyphenols, squalamine and trodusquemine were shown to inhibit α-syn aggregation in vitro and in vivo [221,222]. Of the previously mentioned disaggregants, brazilin is able to inhibit Aβ, α-syn, and IAPP aggregation, and tanshinone I and II are able to inhibit Aβ and α-syn aggregation [200–204].

Anti-amyloid small molecules with no natural product basis have also been developed. The compounds niclosamide, 10058-F4, AMG, TNP, TBB, and DMS were shown to inhibit variant Htt aggregation in vitro [223]. Another small molecule, PE859, was found to act as a tau aggregation inhibitor [224]. Other small molecules that are capable of inhibiting tau aggregation have been designed based on the rhodanines, anthraquinones, N-phenylamines, and phenylthiazolylhydrazides [225–228].

The small molecule CLR01 is known as a molecular tweezer and works via binding to exposed lysine residues [229]. CLR01's binding energy with lysine is considerably lower than the binding energies found in normal proteins, which leads to higher specificity towards lysine residues that take part in weaker interactions, such as those on amyloidogenic proteins that contribute to abnormal protein aggregation [230]. CLR01 was found to reduce the aggregation of multiple amyloidogenic proteins, including tau aggregation in a tauopathy mouse model, Aβ in an AD mouse model, SOD1 both in vitro and in an ALS mouse model, α-syn in a synucleinopathy mice model, variant Htt aggregation in vitro, and IAPP aggregation in vitro [231–237]. Adverse effects on normal protein assembly were not observed in vitro until 55 times the normal dose was administered, and mice were able to survive 2500 times the normal dose. CLR01 was found to have low blood–brain barrier permeability, but the amount of molecule that did reach the brain remained for three days [230].

12. Peptide Inhibitors of Amyloidogenic Protein Aggregation

Along with anti-amyloid small molecules, anti-amyloid peptides have also been developed and tested. These peptides act via inhibition of amyloid formation. By using the VQIINK and VQIVYK residues in tau, which have been identified as drivers of its aggregation, tau aggregation inhibitor peptides were designed. These peptides are able to cap tau fibril ends and prevent further fibril growth. Peptides designed to target either of these aggregation-driving residues were shown to inhibit tau aggregation and seeding in vitro, with effectiveness varying based on the specific sequence of the inhibitors [238,239]. Peptides that inhibit Aβ aggregation have also been developed using the residues present in Aβ's self-assembly region. By designing peptides that mimic the self-assembly region of Aβ but contain proline, β-sheet inhibitor peptides were designed that were able to inhibit Aβ fibril formation as well as to disaggregate preformed fibrils [240,241]. Variation in Aβ (1–28) with cyclized residues 17–21 was found to inhibit Aβ40 amyloid formation; however, it did not have an effect on Aβ40 aggregation [242]. Peptides that act as TTR aggregation inhibitors were also designed based on aggregation driving-residues found in the sequence of TTR [243].

It is important to note that peptide inhibitors have many challenges associated with them that small molecules and other types of therapeutics are less likely to face. Peptides are typically more susceptible to enzymatic degradation, have shorter half-lives in comparison to other types of drugs, and have more limited blood–brain barrier permeability [244,245]. Additional optimization must be undertaken when designing peptide inhibitors to extend pharmacokinetic profiles while maintaining their ability to bind to their target. The pepti inhibitors must also be formulated to resist aggregating themselves, especially since peptides may require storage at high concentrations and exposure to other conditions that can make them even more prone to aggregation. These challenges can be overcome but require investment in formulation chemistry teams, and delivery methods such as through liposomes. Peptide drugs remain a viable modality with potential to become powerful medications for targeting amyloid diseases [246,247].

13. Monoclonal Antibodies

The only disease-modifying therapies for AD currently are anti-Aβ monoclonal antibodies (mAb). Notably, the mechanism of action by anti-Aβ mAbs involves amyloid plaque elimination. Of these, lecanemab (Leqembi) and donanemab (Kisunla) have received FDA approval for the treatment of Alzheimer's disease. Lecanemab received accelerated approval in January 2023 followed by full approval in July 2023, and donanemab was approved in July 2024. Aducanumab (Aduhelm) was another anti-Aβ monoclonal antibody that received accelerated approval in 2021; however, it was voluntarily discontinued in 2024 by its manufacturer.

While lecanemab and donanemab expanded the repertoire of mAbs beyond aducanumab, aducanumab offered unprecedented insight into the mechanism of aggregate elimination by mAbs [248,249]. Aducanumab is a mAb that binds to the Aβ N-terminus and has preferential binding to Aβ oligomers and fibrils [250,251]. It has been shown to clear Aβ in transgenic mouse studies. Upon treatment with aducanumab, the clearance of deposits of Aβ was observed alongside an increase in recruitment of microglia. These findings suggest that microglial recruitment may contribute to plaque clearance following antibody binding. However, the relative contributions of direct fibril destabilization versus microglia-mediated phagocytosis remain an area of active investigation [252]. Lecanemab is an antibody that preferentially binds to Aβ protofibrils and was found to inhibit the formation of fibrils both in vitro and in mouse brains [252,253]. In Phase II and Phase III clinical trials, lecanemab was shown to significantly reduce Aβ and slow the decline in cognitive abilities in early AD cases [254,255]. Donanemab is a mAb that binds selectively to an epitope only present in Aβ plaques [256]. Donanemab was shown to reduce amyloid deposits as well as slow cognitive and functional decline to a degree in early AD. It is probable that the management of additional dementia progression requires earlier intervention with anti-amyloid antibodies and/or combination with medications targeting tau co-pathology. Aβ40 and Aβ42 plasma levels were unaffected following treatment with donanemab, suggesting that the mAb is acting directly on Aβ plaques [257,258].

Anti-Aβ antibodies are also associated with amyloid-related imaging abnormalities (ARIA), which include brain swelling and small hemorrhages and are thought to result from the antibody-mediated clearance of amyloid deposits in cerebral blood vessels. These events highlight an additional safety consideration when developing or testing therapeutic strategies that promote amyloid clearance [259]. For example, during Phase II clinical trials for donanemab, if an ARIA was observed within the first three doses, the dose given was not increased [258].

Clues about where and how drug molecules can fail come from molecular and clinical studies. Anti-Aβ mAbs that have struggled or failed in clinical trials, such as crenezumab,

were not shown to have a significant effect on slowing cognitive or functional decline. However, crenezumab was shown to inhibit Aβ aggregation and promote Aβ disaggregation. Inhibition of Aβ aggregation is thought to occur via the binding of crenezumab to amino acids in Aβ that are necessary for further aggregation, as well as via the disruption of Aβ's hairpin turn [260]. One proposed explanation for the limited clinical efficacy of crenezumab relates to its weaker specificity for a specific Aβ species when compared to another successful mAb, such as the previously mentioned lecanemab and donanemab. Lecanemab's binding specificity for protofilaments and other oligomers is over 1000-fold compared to its binding to Aβ monomer, and donanemab showed no binding to other Aβ species apart from plaques [251–254]. In comparison, crenezumab is able to bind to multiple Aβ conformations, with 10-fold greater affinity for oligomers in comparison to monomers [261]. This binding profile may limit crenezumab's ability to effectively clear Aβ plaques or Aβ species that contribute more strongly to plaque formation, and therefore limit its ability to show an effect on cognitive decline, especially in comparison to the previously mentioned antibodies that were clinical successes.

It was also shown that the single-chain variable fragment (scFv) region of the mAbs crenezumab, solanezumab, and 12B4 is able to disaggregate Aβ42 in vitro, but the scFV based on crenezumab was shown to have this disaggregation activity to a greater degree. This may be due to crenezumab having more favorable binding to Aβ oligomers and fibrils [262]. A different study showed that mAbs containing an N-terminal Aβ epitope were able to disaggregate Aβ fibrils into oligomers. However, these oligomers were found to have increased toxicity [263]. This study highlights a potential risk associated with therapeutic strategies that disaggregate amyloid fibrils. Partial disaggregation can generate oligomeric species that are believed to be more toxic than mature fibrils, such as that observed with N-terminal Aβ epitope-containing mAbs [263,264]. These findings should be taken into consideration when testing and developing small-molecule or protein disaggregases across amyloid diseases in the future. These findings also underscore the critical need for a more detailed and granular understanding of how specific drug molecules and their concentrations influence the formation of molecular species resulting from disaggregation.

Monoclonal antibodies are also being developed for the treatment of other amyloid diseases; however, none have yet reached the market. The mAb PRN100 is the humanized form of the mAb ICSM18, which was designed to bind to PrP^{C} and prevent it from converting to the PrP^{SC}, the disease-related aggregated isoform [265]. ICSM18 was found to reduce PrP^{Sc} levels and infectivity in mouse models [266]. A small clinical study with CJD patients showed that PRN100 was able to reach the brain and that PRN100 did not lead to significant adverse events. The scope of this study was too small to determine efficacy in the treatment of CJD, and future clinical trials will have to be performed to determine this [267]. Anselamimab is another monoclonal antibody under investigation in the treatment of AL amyloidosis. Anselamimab targets a conformational neoepitope present on misfolded light chains, with studies in mouse models finding that these light chain amyloid deposits were cleared via the recruitment of macrophages [268–271]. Anselamimab finished Phase III clinical trials and failed to see significant results with regard to the primary endpoint when analyzing the total patient population. However, the manufacturer, AstraZeneca, stated that promising results were seen when it came to survival and hospitalization in a specific undisclosed patient subgroup, and that the results from these trials are undergoing further evaluation before being shared. Because these findings were derived from post-study subgroup analyses rather than the prespecified primary endpoint, and because no data has been shared yet to support the manufacturer's claims, the validity of this statement remains uncertain and will require confirmation in future studies or analyses [272]. ALXN2200 is a monoclonal antibody that binds to an epitope present in both wild-type and variant

TTR that is usually covered in its non-aggregated form. ALXN2200 was found to facilitate the removal of ATTR aggregates via macrophages in mouse models, as well as ex vivo in patient cardiac tissue [273]. ALXN2200 is currently undergoing Phase III clinical trials (NCT06183931).

Cinpanemab (BIIB054) is a monoclonal antibody that targets the N-terminal region of α-syn, with high selectivity towards α-syn aggregates. Preclinical data in transgenic mouse models showed that treatment with BIIB054 reduced truncated α-syn in the contralateral cortex and delayed the onset of paralysis [274]. However, cinpanemab failed to demonstrate efficacy in clinical trials for the treatment of early-stage PD [275]. MEDI1341 (TAK-341) is another anti-α-syn mAb; it targets the C-terminus of both monomeric and aggregated α-syn and is able to sequester extracellular α-syn. Preclinical studies have shown that MEDI1341 is able to reduce α-syn levels in the cerebrospinal fluid and interstitial fluid of mouse models [276]. MEDI1341 is currently undergoing Phase II clinical trials for the treatment of MSA [277]. α-miSOD1 is a mAb that selectively targets misfolded SOD1, which is the species prone to aggregation and amyloid formation in ALS. Following treatment with α-miSOD1, transgenic mice containing SOD1 variants linked to ALS were shown to have reduced SOD1 aggregation and were able to retain motor function and survive for longer compared to the control mice [278]. A mAb that selectively targets hIAPP oligomers (α-IAPP-O) was also developed. Type 2 diabetes transgenic and human-islet grafted mice treated with α-IAPP-O had reduced amyloid formation and beta cell toxicity [279].

While it remains unclear to what extent anti-amyloid mAbs disaggregate amyloid fibrils on their own, evidence suggests a converging mechanism of action for multiple mAbs involving amyloid elimination through mAb binding and interaction with biological degradation mechanisms, such as microglial or macrophage-mediated phagocytosis. Aducanumab and α-miSOD1 demonstrate increased recruitment of microglia or macrophages respectively alongside the clearance of aggregates, while α-IAPP-O and the anti-tau mAb MC1 lose effectiveness in clearing aggregates with forms lacking the Fc region or Fc glycosylation, suggesting that recruitment of microglia plays an important role in their activity [251,278–280]. These antibodies are thought to lead to phagocytosis of fibrillar or misfolded protein aggregates and degradation through the endosomal–lysosomal system. It is important to keep in mind that the therapeutic effectiveness of microglia and macrophage-mediated clearance mechanisms may be influenced by age-related changes in microglial and macrophage function. Aging is associated with the dysregulation of both of these systems, which may limit the efficiency of antibody-mediated amyloid clearance in older patients [281,282]. Despite this, multiple clinical and experimental analyses have shown that this process is still able to result in a reduction in amyloid plaques and protein aggregates that are linked to disease progression. Successes with anti-amyloid mAbs suggest disaggregases might be well suited to similarly prime other types of amyloid fibrils for degradation via intracellular proteostasis pathways, such as UPS or autophagy–lysosomal pathways.

14. Gene Silencing Therapeutic Approaches

In addition to antibody-based therapies, gene-silencing strategies have emerged as important complementary approaches for amyloid diseases. Antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) therapeutics reduce the production of aggregation-prone proteins at the transcript level and therefore act upstream of proteostasis mechanisms. For example, the RNA interference therapeutic patisiran and the antisense oligonucleotide inotersen have demonstrated clinical efficacy in transthyretin (TTR) amyloidosis by lowering circulating TTR levels and slowing disease progression [283,284]. Similar approaches have been explored for HD through ASOs targeting mutant huntingtin tran-

scripts. One of the most studied candidates is tominersen, designed to bind the expanded CAG repeat region in HTT mRNA and reduce production of the huntingtin protein. In a Phase I/IIa study, patients receiving periodic dosing over approximately 15 months showed an initial increase in cerebrospinal fluid neurofilament light chain (NFL), followed by a subsequent decrease despite continued treatment [285,286]. However, the Phase III trial initiated in 2019 was halted in 2021 after interim analyses indicated that patients receiving tominersen every eight weeks experienced worse clinical outcomes and more adverse events than those receiving placebo. The failure of tominersen in Phase III trials highlights important mechanistic considerations, including the possibility that treatment was initiated at an advanced stage of neurodegeneration, and/or that the non-selective suppression of both mutant and wild-type huntingtin may compromise essential neuronal functions [287,288]. In PD, antisense strategies targeting the SNCA transcript have been shown to reduce α-syn production and attenuate pathology in rodent preformed fibril models of Parkinson's disease [286,289]. Similar concepts are being investigated for AD, although these remain at the preclinical stage. Several ASOs aim to lower amyloid-β (Aβ) production by targeting the mRNA encoding amyloid precursor protein (APP) or enzymes involved in amyloidogenic processing pathways [286,290]. By reducing the synthesis of aggregation-prone proteins, these strategies may complement proteostasis-modulating therapies that enhance aggregate clearance.

15. Conclusions and Future Perspectives

Proteostasis plays a vital role in maintaining cellular integrity, and disruptions in protein quality control are central to the onset and progression of various protein folding diseases, including several forms of neurodegeneration and systemic amyloidosis. This review has summarized the current understanding of proteostasis impairments in these conditions and highlighted ongoing efforts to restore its function (Figure 3). The evidence presented underscores a central link involving dysfunction of UPS, autophagy, and chaperone systems across amyloid-related diseases. When these systems are compromised, they not only fail to prevent protein aggregation but also exacerbate it, becoming actively detrimental rather than protective to the cell.

Small-molecule disaggregases targeting pathogenic aggregates could rescue multiple processes that otherwise drive a feed-forward cascade of proteostasis failure. Within the UPS, aggregated forms of amyloid-β, tau, α-synuclein, and huntingtin directly inhibit proteasome activity by interacting with the 19S regulatory particle and preventing gate opening of the 20S catalytic core. Effective disaggregation of these fibrils would relieve this structural blockade and restore native UPS function. Moreover, because the proteasome degrades protein aggregates less efficiently compared to protein monomers, the proteasome can aberrantly fragment aggregates into toxic, seeding-competent intermediates. By remodeling aggregates into structures that are more amenable to degradation, disaggregases may improve the degradation of protein aggregates by the endogenous UPS.

Similarly, disaggregases may also benefit aggregate-mediated disruptions in the autophagy–lysosomal pathway. Both tau and α-synuclein aggregates disrupt autophagosome–lysosome fusion by interfering with ESCRT-III, compromising endolysosomal membrane integrity. Additionally, acetylated tau impairs chaperone-mediated autophagy by preventing translocation to the lysosome. Disaggregases may help restore autophagic function, enabling more effective aggregate degradation.

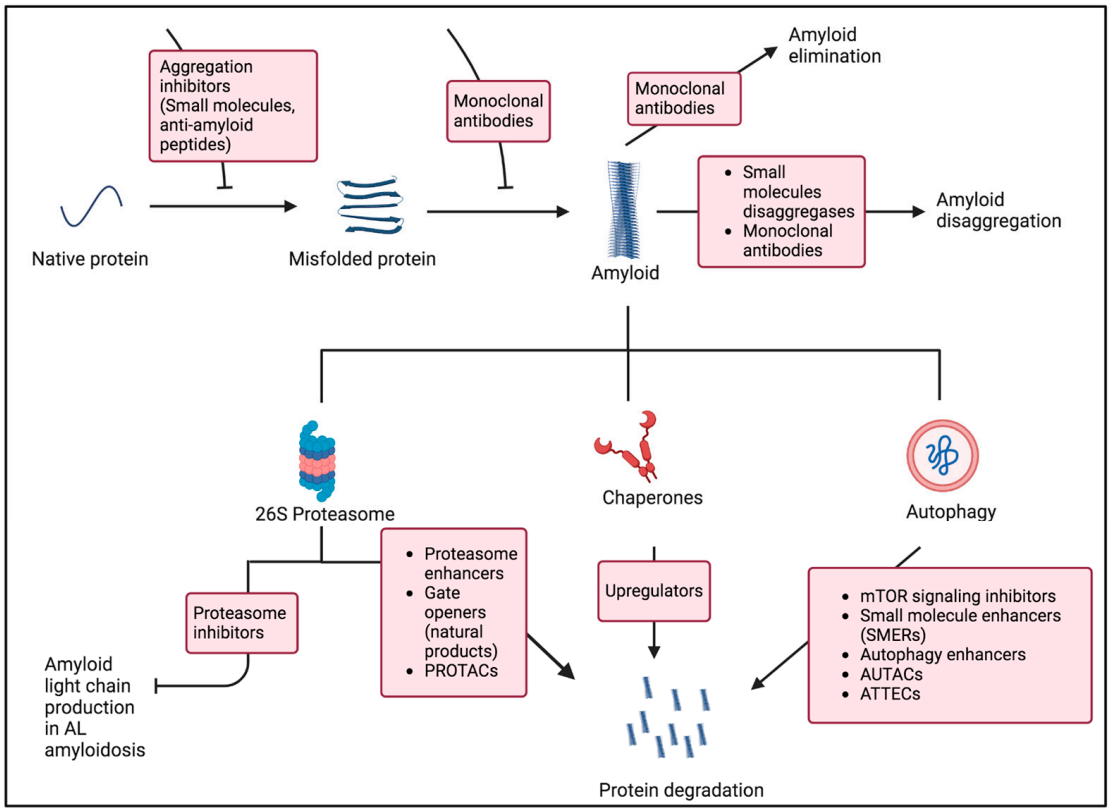


Figure 3. Therapeutic strategies to restore proteostasis. Several therapeutic agents have been studied to prevent amyloid formation, induce amyloid disaggregation/elimination or enhance the proteolytic activity of cellular quality control systems such as UPS, autophagy and molecular chaperones. Created in BioRender. Albanese, A. (2026). BioRender.com/b59l203.

Finally, endogenous molecular chaperones, such as VCP, can act as a 'double-edged sword,' inadvertently exacerbating disease through incomplete disaggregation into toxic seeds. By enhancing disaggregase activity to overcome the bimodal effects of endogenous degradation and chaperone systems, disaggregases have the potential to promote the efficient disassembly and clearance of protein aggregates by synergizing with macromolecular chaperone systems.

Based on the evidence reviewed here, the conceptual framework we propose emphasizes that protein aggregation drives systemic proteostasis failure involving the breakdown of multiple coordinated activities involving UPS, autophagy, and molecular chaperones. Pharmacological strategies involving small molecule disaggregants may address multiple aspects of impaired proteostasis, helping to re-establish functional crosstalk between degradation and folding systems so they can work synergistically both to resolve protein aggregates and restore proteomic fidelity.

This review has also examined diverse therapeutic strategies aimed at restoring proteostasis, including modulators of UPS, autophagy, and chaperone activity, as well as amyloid disaggregases and inhibitors in the form of small molecules, peptides, and monoclonal antibodies (Table 1). Collectively, these approaches highlight the growing repertoire of molecules that provide targeted interventions necessary for rescuing proteostasis dysfunction in the context of protein aggregation diseases.

Table 1. Non-exhaustive list of agents that enhance the elimination of amyloid aggregates.

Amyloid Disaggregant/Inhibitor	Amyloid Target	Reference
Small molecules (Natural products)		
Curcumin	Aβ, tau, α-syn, TTR	[188,189,191–193,218]
EGCG	Aβ, tau, α-syn, TTR, Htt variant	[193–196,219,220]
Ginnalin A, Myricetin, Morin, Quercetin, Catechin, Epicatechin, Kaempferol	Aβ	[197,198]
Baicalein, Delphinidin, Exifone, Gallocatechin gallate, Gossypetin, Theaflavine	Aβ, tau, α-syn	[219]
Epigallocatechin, Gallocatechin, Myricetin, Rosmarinic acid, 2,3,4-trihydroxybenzophenone	Aβ, tau, α-syn	[219]
Catechin gallate, Luteolin	Aβ	[219]
Brazilin	Aβ, α-syn, hIAPP	[200–202]
Tanshinone I and II	Aβ, α-syn	[203,204]
Squalamine, trodusquemine	α-syn	[221,222]
DHM	tau	[199]
Dopamine, L-dopa	tau	[205]
Penicillic acid	tau	[212]
Small Molecules (Other)		
CNS-11	tau, α-syn	[196,206]
CNS-12	tau	[206]
Tafamadis, acoramidis *	TTR	[213–215]
Niclosamide, 10058-F4, AMG, TNP, TBB, DMS	Htt variant	[223]
PE859	tau	[224]
CLR01	tau, Aβ, SOD1, α-syn, Htt variant, IAPP	[231–237]
Peptides		
Tau aggregation inhibitor peptides	tau	[238,239]
β-sheet breaker peptides	Aβ	[240,241]
cyclo^{17,21}-[Lys^{17}, Asp^{21}]Aβ(1–28)	Aβ	[242]
TTR aggregation inhibitor peptides	TTR	[243]
Monoclonal antibodies		
Aducanumab	Aβ	[250,251]
Lecanemab *	Aβ	[252,253]
Donanemab *	Aβ	[256]
Crenezumab	Aβ	[260]
PRN100	PrP	[265]
Anselamimab	AL light chain amyloids	[268–270]
ALXN2200	TTR	[273]
Cinpanemab	α-syn	[274]
MEDI1341	α-syn	[276]
α-miSOD1	SOD1	[278]
α-IAPP-O	hIAPP	[279]

*: indicates small molecules or monoclonal antibodies that have successfully passed clinical trials and are used as active therapeutics.

Future research should focus on identifying the mechanistic determinants that govern aggregate formation, processing, and clearance. Importantly, the effectiveness of proteostasis-targeting interventions may depend on the stage of disease progression. Strategies that prevent early aggregation or oligomer formation may differ in their effects once mature fibrils and secondary pathologies have developed, and therapeutic agents such as small molecules or monoclonal antibodies may exhibit different binding specificities depending on aggregate conformation. Likewise, endogenous proteolytic systems may process distinct aggregate species with varying efficiency.

Defining the structural determinants that drive aggregate fragmentation versus complete proteolytic clearance will therefore be essential. Structural and biophysical characterization of aggregate species, combined with systematic screening of disaggregases and small-molecule modulators, may help clarify these mechanisms. In addition, determining whether small molecules can remodel aggregates into forms more amenable to endogenous degradation represents a promising direction for therapeutic development. By elucidating how specific molecules influence proteostasis, prion-like seeding, protein aggregation, and degradation, researchers can uncover critical determinants of therapeutic efficacy. Ultimately, such insights may enable the rational design of chemical and macromolecular disaggregases that enhance aggregate clearance while preventing the formation of toxic seeds by simultaneously restoring and working synergistically with endogenous proteostasis pathways.

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