Protein Misfolding Across Neurodegenerative Diseases: Comparative Mechanisms of Tau, α-Synuclein, and Prion Protein Aggregation and Their Therapeutic Implications

Amara Ranjit Kamble[1], Basina Padmini[2], Rupak Roy[2]
[1]*Sancta Maria International School, Telangana 500019, India.*
[2]*SHRM Biotechnologies Pvt. Ltd., Kolkata- 700155*

***Abstract*—Neurodegenerative disorders are a broad spectrum of progressive diseases characterized by the degeneration of neurons, synapses, and eventually the death of nerve cells. Regardless of differences in symptoms, progression, and brain areas affected, these disorders often share a common feature: the incorrect folding and buildup of specific proteins. Tau, α-synuclein, and prion protein, respectively, are examples of various proteins that can follow similar pathways to promote neurodegeneration in the brain. In physiological circumstances, tau helps stabilize microtubules and facilitates axonal transport, whereas α-synuclein serves an essential aspect in the functioning of neurons and synapses. Prion diseases are caused by the conversion of the normal cellular prion protein, PrP^C, into the pathogenic PrP^Sc. These proteins are prone to misfolding, which may generate oligomers and β-sheet-rich fibrils with the potential to disrupt the cell signaling pathways of synapses, axonal transport, mitochondrial function, membrane composition, protein clearance pathways, and cellular stress response systems.**

One important property that they share is their ability to self-assemble in a seed-dependent manner. The misfolded proteins cause a conformational shift in normally folded proteins, so pathology spreads from one section of the brain to another and from one cell to another.

However, tau and α-synuclein, while sharing prion-like features, vary from classic infectious prions in their specific biochemical, genetic, and clinical characteristics. Furthermore, a direct relationship and cross-seeding between tau and α-synuclein have been reported, indicating that neurodegenerative diseases may be characterized by linked misfolding processes rather than by entirely separate systems. These results have important therapeutic implications. Current strategies aim to inhibit pathological protein modification and aggregation, reduce toxic soluble oligomers, block cellular uptake and spread, selectively target aggregates, enhance or modulate proteasomal and autophagic clearance, and employ mAbs or similar agents to bind, neutralize, or enhance the clearance of toxic protein species. To summarize, the increased understanding of tau, α-synuclein, and prion protein demonstrates that the mechanisms of disturbed proteostasis, templated misfolding, conformational change, and propagation of aggregation are common mechanisms that can be targeted therapeutically in neurodegenerative disorders.

***Index Terms*—neurodegeneration, protein misfolding, tau, α-synuclein, prion protein, prion-like propagation, cross-seeding, proteostasis.**

I. INTRODUCTION

1.1. Overview of Neurodegenerative Diseases

Neurodegenerative illnesses are a heterogeneous group of chronic diseases characterized by neuronal malfunction and degeneration in specific areas of the central and peripheral nervous systems. Neuronal degeneration causes progressive loss of the reflex arcs and circuits in which the neurons participate. This leads to a gradual loss of cognition, mobility, behavior, autonomic function, or a combination of these [1, 2]. Neurodegeneration is generally a slow process of progression. Molecular or cellular problems associated with neurodegeneration may be physiologically asymptomatic until symptoms develop. These early cellular and molecular events are necessary for understanding disease progression and treatment approaches. This is because the pathogenic changes in proteins may predate signs of brain injury by years [1].

Infectious spongiform encephalopathies or prion

diseases, including kuru, Creutzfeldt-Jakob disease (CJD), and Gerstmann-Sträussler-Scheinker syndrome (GSS), are one group of neurodegenerative disorders. Other major neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [2, 3].

1.2. Protein Homeostasis in Neurones

Protein homeostasis (proteostasis) is the maintenance of a functional proteome by the coordination of mechanisms required for protein synthesis, folding, transport, quality control, and destruction [4]. The folding of newly synthesised polypeptides begins during translation and continues after synthesis by adopting functional three-dimensional conformations, or the native state [5].

Molecular chaperones of the Hsp70, Hsp90, and Hsp60 families are capable of binding to and assisting unfolded and partially folded proteins to prevent their making incorrect contacts and to attain stable conformations [5, 6]. If a protein fails to fold into its native structure, cellular quality-control procedures usually remove it. There are two major degradation systems: the ubiquitin-proteasome system (UPS) and the autophagy-lysosome system. In the UPS, ubiquitin is conjugated onto damaged or misfolded proteins and marks them for proteasomal destruction.

Autophagy is particularly important for removing large clumps of proteins and damaged organelles. For example, cellular waste can be sequestered into double-membraned autophagosomes and then fuse with lysosomes for degradation. Most neurons are post-mitotic and cannot dilute damaged proteins via cell division. This process would account for the accumulation of protein aggregates in some brain regions and the unique importance of quality control mechanisms in nervous tissue [7, 8].

Their lengthy axons and large dendritic networks, as well as their extremely polar shape, also require precise protein trafficking and constant maintenance [7]. Therefore, autophagy is a critical process for neuronal survival, and its dysfunction has been linked to protein aggregation in AD, PD, and ALS [7, 8]. Furthermore, some neuronal populations have extremely high energy requirements that may impact their vulnerability to degeneration [1]. When protein production, folding, refolding, trafficking, or degradation become uneven, this process might be thrown off balance. Abnormal protein accumulation may then disrupt the proteasomal and autophagic processes, creating a feedback loop in which clearance failure results in additional aggregation.

1.3. Proteinopathies

Proteinopathies are diseases that are generally described by proteins demonstrating abnormal folding, buildup of aggregates, or processing. Proteinopathies can be caused by proteins that are unrelated in their natural conformation and function but exhibit common pathological properties, such as seeding behavior, oligomer and fibril formation, and gradual spread of pathology to other proteins [2, 3]. Major neurodegenerative disorders are often grouped in representative proteinopathies according to disease-protein correlations revealed in the reviewed literature [1, 2, 3]. The concept of proteinopathies is relevant, as abnormal protein assemblies are not necessarily restricted to their cell of origin. Aggregates can serve as conformational templates that promote the self-assembly of other proteins, thereby facilitating the propagation of misfolding to neighboring cells or related brain regions [2].

Table 1. Major pathological proteins associated with selected neurodegenerative diseases

Neurodegenerative Disease or Group	Major Pathological Protein	Characteristic Pathology
Alzheimer's Disease	Amyloid-β, tau	Intracellular tau neurofibrillary lesions and
		extracellular amyloid plaques [2, 3]
Parkinson's Disease	α-Synuclein	Lewy bodies and Lewy neurites [9]
Multiple System Atrophy	α-Synuclein	Mostly cytoplasmic

		inclusions in glia [10]
Dementia with Lewy bodies	α-Synuclein	Lewy pathology of neurons extensively [9]
Tauopathies, including PSP, CBD, and Pick's disease	Tau	Intracellular tau clumps are abnormal [16]
Huntington's disease	Mutant huntingtin	Polyglutamine-rich huntingtin aggregates [2]
ALS	TDP-43, SOD1, FUS	Abnormal protein inclusions, especially in motor neurons [2]
Prion diseases	PrP^Sc	Conversion of pathogenic prion protein and its self-perpetuating accumulation [27]

1.4. Rationale for Selecting Tau, α-Synuclein, and Prion Protein

The selection of tau, α-synuclein, and prion provides a useful platform for comparing the three protein-associated neurodegenerative disease processes. These proteins are different in structure, localization, and clinical context but share key features such as seed-dependent misfolding,

progressive propagation, aggregation, and accumulation of pathogenic assemblies. But at the same time, this comparison has a major drawback.

Similar concepts, such as “seeding” or "propagation" are not always founded on the same fundamental principles for various diseases [11, 14].

Tau is, for the most part, a marker of neurofibrillary illness intracellularly. Tau is involved in microtubule assembly and stabilization, axonal maintenance, and intracellular transport [16].

Pathological changes, such as hyperphosphorylation, diminish tau binding to microtubules and promote tau polymerization into paired helical filaments and neurofibrillary tangles [16].

α-Synuclein is a unique paradigm with a disease involving both neuronal and glial synucleinopathies. Pathogenic α-synuclein is closely linked to Lewy bodies and Lewy neurites in neurons in Parkinson’s disease and dementia with Lewy bodies. Conversely, α-synuclein predominantly deposits in the form of glial cytoplasmic inclusions in multiple system atrophy [9, 10, 11]. So the same protein can potentially contribute to different disease manifestations depending on the cellular environment. The biggest commonality is the prion protein. In prion diseases, normal cellular prion protein, PrPC, interacts with misfolded PrPSc, inducing a conformational shift into a pathogenic form that is rich in β-sheets [27, 29]. This form leads to a self-reinforcing cycle of repeated conversion. PrPSc is the molecular cause of true transmissible prion disease [27]. Prion-like proliferation and seeding of tau and α-synuclein allow pathological conformations to associate with normally folded proteins and encourage the progressive spread of aggregation between cells and interconnected brain regions [11, 14].

II. MOLECULAR BASIS OF PROTEIN MISFOLDING

2.1. Normal Protein Folding

The function of a protein is greatly dependent on its ability to obtain and maintain a proper three-dimensional structure. The first step is the fundamental structure, the sequence of amino acids that make up the polypeptide chain. As the chain forms during translation, distinct areas can interact and generate stabilizing bonds, so folding can start co-translationally and continue after synthesis [5]. These interactions give rise to secondary structures, notably α-helices and β-sheets, which are stabilized by hydrogen bonds between groups in the polypeptide backbone

[12]. Further folding results in tertiary structure, in which secondary structural pieces are folded into a more complicated three-dimensional conformation. This structure is stabilized by several molecular interactions. Hydrophilic areas are exposed, and hydrophobic residues from amino

acids are normally buried away from the watery cellular environment [12].

The natural structure is the spatial arrangement that allows the protein to carry out its biological activity efficiently. Ionic interactions between charged groups, hydrogen bonding, van der Waals forces, and, in some proteins, covalent disulfide bonds [12] stabilize this structure.

2.2. Protein Misfolding

Misfolded proteins could expose regions that are normally hidden in the properly folded conformation. Therefore, they may interact abnormally with organelles, membranes, and other proteins [12]. There are several circumstances that can destabilize a protein's structure. Mutations can affect the primary structure or the metabolic and processing pathway directly [1].

Post-translational changes can also affect the behavior of proteins. For example, hyperphosphorylation, cleavage, glycosylation, ubiquitination, nitration, and glycation of tau are known to occur (the latter being especially relevant as they can switch tau from normal microtubule binding to pathological self-association [3, 16]).

2.3. Protein Aggregation

Aggregation is not an event; it is a multi-stage process, as described in Section 2.3. Primary nucleation, the gathering of particular monomers to form a stable nucleus, takes place first. Elongation occurs, with more protein monomers being added to the developing structure. Other mechanisms proposed include secondary nucleation and fibril fragmentation [13]. Both procedures generate novel sites for aggregation and can promote the rate of aggregation in the presence of fibrils [13]. This is important because medications inhibiting early nucleation may not affect further spreading via fragmentation [13]. Oligomers are small soluble clumps that can form. These oligomers may be extended to protofibrils and eventually evolve to large fibrillar assemblies [47, 49].

Many pathogenic fibrils develop an amyloid form in which the β-sheets are arranged in the cross-β orientation [47], as described in section 2.3.

However, the eventual insoluble fibril is not necessarily the only “harmful” conformation. Different soluble oligomeric intermediates that can arise may have various levels of neurotoxicity and solubility. Different structural strains of the same aggregate have varied biological ramifications [46, 47, 49]. When many aggregates have evolved, they can become seeds. These seeds can bind to normally folded proteins and trigger their conversion into the pathogenic aggregation state [14]. The aggregation develops with the addition of more misfolded monomers. This leads to a self-accelerating build-up [14]. This seeding activity and templated misfolding is the molecular basis of prion disease, and comparable mechanisms are validated by prion-related proteins, including tau and α-synuclein [11, 14, 27].

2.4. How Protein Aggregation Damages Neurons

Protein aggregates injure neurons through a multitude of overlapping routes rather than one unique process. Pathological fibrils or oligomeric proteins could cause problems with synaptic function by impacting neurotransmitter release, synaptic organization, or receptor activation [7, 46]. Tau disease may destabilize microtubules and disrupt axonal transport (the flow of chemicals and organelles down the axon). This transport deficiency may cause greater widespread synaptic dysfunction over time [16]. Aggregated proteins can also be focused on mitochondria, resulting in reduced energy production in the cell and higher levels of oxidative stress. Subsequently, reactive oxygen species can damage other proteins, leading to more misfolding and an increase in the cycle of oxidative injury [7, 22, 23]. Abnormal protein species may also interact with cell membranes, affecting the organization of membrane receptor-associated signaling and permeability [46, 47].

Aggregation also aggravates neuroinflammation. It has been shown that misfolded proteins stimulate activation of microglia and astrocytes to create stress molecules and inflammatory cytokines [4, 36]. Short-term stimulation might be useful to remove the aberrant aggregates, but continuous activation leads to chronic inflammation and increased neuronal and proteostatic stress [36]. Impaired synaptic function, oxidative stress, axonal transport failure, neuroinflammation, quality control failure, and membrane disruption act in concert to reduce neuronal function and survival. These pathways are complementary and cause irreversible neuronal malfunction and death [4, 7, 16, 36].

III. TAU MISFOLDING IN ALZHEIMER'S DISEASE

Tau is an extremely soluble microtubule-associated protein that is distributed throughout the nervous system and is present in very high quantities in neuronal axons. Under physiological conditions, tau associates with microtubules and participates in their regulation, stabilization, and assembly. Tau helps to keep microtubule networks intact, allowing vesicles, proteins, and organelles to travel between neuronal cell bodies and synaptic terminals to support axonal structure [16]. Human tau is encoded by the MAPT gene and produced as several isoforms by alternative splicing. The isoforms differ in the presence of N-terminal inserts and in the number of microtubule-binding repeats (three or four), resulting in 3R and 4R tau isoforms. Different tauopathies have different isoforms; e.g., Alzheimer's disease (AD) usually contains both 3R and 4R tau [15].

Post-translational changes of tau, including acetylation, ubiquitination, glycosylation, nitration, cleavage, phosphorylation, and glycation, dramatically modulate its function [3, 16].
Phosphorylation is particularly significant, as the normal microtubule-binding properties of tau depend on its phosphorylation state. Tau is phosphorylated by various kinases such as glycogen synthase kinase 3β (GSK3β) and cyclin-dependent kinase 5 (CDK5) and is dephosphorylated by phosphatases such as protein phosphatase 2A (PP2A). Phosphorylation per se is not damaging, and reversible phosphorylation is a normal regulatory process for tau. But when phosphorylation is excessive or chronically aberrant, it becomes an issue. Under such conditions, tau has lower affinity for microtubules, and hence more soluble tau is available to participate in pathogenic interactions [2, 16].

When tau leaves microtubules, two things could be happening at once. First, the typical function of tau in stabilizing the microtubules within the neurone is lost. Second, aberrant tau is more prone to self-association. The tau molecules may then aggregate into soluble oligomers and mature into larger-sized fibrillar structures and produce pathogenic assemblies such as paired helical filaments and neurofibrillary tangles, hallmarks of Alzheimer's disease [15, 16]. This creates a self-sustaining loop, with tau dissociation generally destabilizing microtubules, and their disassembly reducing axonal shape and transit. But the formation of aggregates does not explain tau neurotoxicity. Diverse conformational forms of tau may have diverse biological significance, and soluble oligomeric intermediates are increasingly identified as essential pathogenic species that impede cellular activities before the emergence of massive fibrillar inclusions [6, 46, 47, 49].

Tau can also adopt various conformations. These conformational variants, known as strains, differ in their degree of biological activity, cell selectivity, and ability to transmit pathology [14, 16]. Once formed, an aberrant tau seed can recruit soluble tau molecules and convert them to aggregation-prone conformations. The newly misfolded tau then joins the developing aggregate, allowing the diseased structure to proliferate [14, 16]. Another way that abnormal tau may spread is from cell to cell, which would accelerate the spread of pathology to interconnected parts of the brain. In Alzheimer's disease, tau pathology generally originates in isolated places and then spreads to more extensive limbic and neocortical regions [17]. That is why tau propagation is called prion-like, but it does not have the same known natural infectivity between individuals as classical prion proteins [14, 17]. These aberrant tau types can also be disrupted [16, 17].

IV. A-SYNUCLEIN MISFOLDING IN PARKINSON'S DISEASE

Synucleinopathies are a group of neurodegenerative disorders; within this category falls Parkinson's disease. α-Synuclein is a relatively small presynaptic protein, which is thought to perform an essential function in the development and pathology of the disease. Under normal bodily conditions, α-Synuclein has been shown to regulate synaptic vesicle transport, vesicle organization, neurotransmitter release, and SNARE-associated cellular processes [18, 19, 20]. α-Synuclein is structurally flexible, rather than a stable globular protein. Structurally versatile,
α-synuclein interacts actively with lipid membranes and proteins, but it may also give rise to pathological self-association [18, 19, 20]. An N-terminal portion, a central hydrophobic core, and a C-terminal area make up the structural domains of the 140-amino-acid protein α-synuclein [20]. These domains control

membrane binding, aggregation, cellular processes, and inter-protein interactions. Under these pathological conditions, soluble α-synuclein undergoes oligomer formation and fibrillar aggregate production, with the latter containing a higher percentage of β-sheet [2, 3, 11, 20]. α-Synuclein aggregates are an important part of Lewy bodies and Lewy neurites in neurons found in PD and dementia with Lewy bodies [9, 11]. If multiple system atrophy occurs, α-Synuclein aggregates mostly occur in oligodendrocytes in the form of glial cytoplasmic inclusions [10, 11].

Plenty of factors can encourage the conversion of α-synuclein into a pathological form. For example, point mutations and gene duplications, when genetic modifications take place, can encourage the aggregation or misfolding of α-Synuclein [2, 4, 20]. Other mechanisms that may contribute are environmental stress and oxidative harm, alterations to the quaternary structure, and failed clearance mechanisms [2, 4]. Post-translational modifications also act as a means of regulation. Post-translational modifications can occur in many ways, such as nitration, glycosylation, phosphorylation, and SUMOylation; these types of modifications have been studied in association with pathological conformations of α-Synuclein [2, 11]. Biomarker and α-synuclein pathology studies depend heavily on phosphorylated forms, namely those that involve serine residues like S129 [2, 11].

Irregular conformations of α-Synuclein can transform soluble monomers into oligomers, as discussed previously [2, 11, 46]. Alternatively, in Tau, the most significant components are not biologically harmful conformations; soluble oligomer forms may inhibit the activities of membranes and synapses before large protofibrils are even formed [46, 47, 49]. Various α-Synuclein fibrils have different thresholds for stress levels and can even adopt different orientations. Differences in the morphology of α-synuclein filaments help in understanding how seeding activity processes, cellular tropism, and disease expression differ even when the pathological protein is the same [2, 11]. They also provide a possible explanation for the functions of the same protein in multiple pathologies, for example, α-Synuclein's role in both Parkinson's disease and multiple system atrophy [2, 7, 11].

α-Synuclein displays seed-dependent activity given its prion-like nature. Endogenous α-Synuclein is aggregated by preformed pathological fibrils, which indicates that irregular pathological structures can associate with normally soluble proteins to form an assembly of pathological aggregates [11, 14].

α-Synuclein pathology is not confined to the brain. Investigation of peripheral α-synuclein pathology and neural pathways has led to the theory of body-first and brain-first subtypes of PD.
The initial site of pathological α-synuclein aggregation may differ between individuals and determine the order of symptom progression [2, 21]. However, gaps in genomic and epidemiological data remain [2, 21].

Neurons can be damaged due to aggregation of α-synuclein via many mechanisms. Aggregates are linked to malfunctioning of the synapse, alterations in mitochondrial activity, oxidative stress, neuroinflammation, and impaired proteostasis [2, 22, 23, 25]. In typical conditions,
α-Synuclein operates at the presynaptic terminals, but when α-Synuclein is in a pathological conformation, its structural abnormalities can directly affect the transit of vesicles and the discharge of neurotransmitter molecules into the synaptic cleft [18, 19, 25]. Mitochondrial abnormalities can lower the amount of energy produced and increase the generation of reactive oxygen species [22, 23, 25], leading to further degradation of proteins and higher levels of misfolding of normal protein molecules [22, 23].

In the very beginning, protein pathology triggers broad cellular stress responses, which cascade into the stimulation of microglial cellular receptors and inflammatory signalling by misfolded forms of α-Synuclein [24, 25, 36]. Disruption of protein clearance cycles boosts the positive feedback loop of aggregation; α-Synuclein is processed by autophagy-lysosomal and proteasomal pathways regularly, so issues in these pathways are strongly linked to the accumulation of pathological aggregates, and irregular α-Synuclein disturbs the UPS pathway. Inadequate autophagic degradation leads to the build-up of oligomers and fibrils [7, 8, 11].

Pathological aggregation can be both a result of proteostasis failure and a cause of its progression [7, 8].

Treatment strategies target various phases of α-synuclein disorder. Both Anle138b and NPT200-11 are examples of small-molecule compounds that have been investigated for their ability to suppress aggregation [2, 37]. Other approaches are aimed at boosting autophagy, enhancing clearance processes, and hindering cellular uptake and proliferation [3, 7]. Blocking or inhibiting endocytic mechanisms and pathways in experiments has provided evidence that regulating uptake can inhibit the transfer of α-Synuclein in experimental models [3, 11].

Monoclonal antibodies (mAbs) like prasinezumab and traditional immunotherapy methods can be used to detect and bind to specific epitopes of α-Synuclein [26]. Others target extracellular α-synuclein to prevent the propagation of pathology between cells [11, 26]. Even in light of these findings, the translation of clinical studies to medical practice is difficult, and mAb therapies have not yet yielded a distinct disease-altering treatment for Parkinson's disease [2, 11, 26].

V. PRION PROTEIN MISFOLDING AND PROPAGATION

Prion disorders are a classic instance of diseases resulting from self-replicating protein conformations [14, 27]. These include prion disorders such as transmissible spongiform
encephalopathies (e.g., Creutzfeldt-Jakob disease) and both genetically inherited and acquired prion diseases [27, 31, 32]. The hallmark change is the structural conversion of the normal cellular prion protein, PrP^C, into PrP^Sc [1, 27].

This change is related to structure and morphology, not genetics. Every new pathological
molecule produced has the same primary structure as PrP^C but has a different pattern of folding [27]. The pathogenic version of PrP binds with endogenous PrP^C to facilitate self-assembly toward an abnormal state with a high beta-sheet character [1, 27].

This process of conformational conversion is done via the use of directive templates [27, 29].

PrP^Sc takes the role of a seed here and associates with PrP^C; the PrP^Sc undergoes elongation by recruiting even more PrP^C and integrating the newly pathological molecules into a growing cluster of assemblies [27, 29]. Smaller fragments of larger aggregates can now act as additional surfaces for seeding, which creates a growing number of active templates; this mechanism can explain how a small pathological conformation of a protein can lead to the spread of pathology across different regions [28–30]. PMCA and other methods of prion amplification play out this concept in vitro by incubating pathological PrP seeds with a much larger quantity of PrP
substrate [28–30]. This process allows conversion and elongation to happen before fibrils are fragmented to create new seeds [29, 30].

The study of prions helps in understanding which aspects of propagation are common and where the proteins differ in progression. This principle remains true, especially for Tau and α-synuclein since both share some parts of the same process [11, 14, 27]. Accumulation of PrP^Sc adds to the progression of neuronal death and dysfunction, but this process, like in other misfolded proteins, occurs through multiple different steps and mechanisms [4, 7, 27]. Misfolded proteins have various effects on surrounding structures; namely, they can impair the function of lysosomes, trigger stress responses in cells, interfere with synaptic connections, disrupt transport within cells, and make membranes unstable [4, 7, 27]. Alongside these effects, glial activation and neuroinflammation signaling can speed up the rate at which neurons degenerate [4, 36].

Prion diseases can also be inherited across generations; this knowledge serves as a means of understanding the implications of genetic variations on how susceptible an individual can be to a neurodegenerative disease and the stability of protein conformations in genetically different individuals [31, 32]. Genetic variations that are pathogenic in nature in the PRNP gene may lead to inherited prion diseases by altering the propensity of PrP to undergo conformational conversion, with different pathological variants giving rise to differences in disease phenotype [31, 32]. More details on specific mutations require a dedicated source for prion-associated genes [31, 32].

Prion disease is particularly hard to treat, as propagation of pathology is dependent on the interactions between pathological and normal versions of PrP [27, 29]. Therapeutic measures can inhibit pathogenic PRP formation and prevent interactions

with both normal and aberrant PRP [3, 7, 27]. Additionally, enhancing clearance systems, disrupting oligomer and fibril formation and growth, and stabilizing cellular normal PRP could all serve as beneficial pathways for treatment [3, 7, 27, 37]. Chemical compounds that can alter beta-sheet formation or assembly in pathological proteins can show anti-prion effects, according to research, though clinical translation is challenging [3, 37]. The strongest practical results of prion research so far have been in improving diagnosis rather than treatment [1, 28, 33]. PMCA and RT-QuIC both strategically use the self-propagating quality of PrP to amplify smaller fragments of seeds in patient samples [28, 29, 33]. RT-QuIC displays strong performance in diagnosing Creutzfeldt-Jakob disease by detecting seeds present in cerebrospinal fluid, with high accuracy and sensitivity [33]. Many similar seed-amplification and detection strategies are now being implemented for α-synuclein, PrP, amyloid-beta, tau, and other pathological proteins [1, 2].

VI. COMPARATIVE MECHANISMS OF NEURODEGENERATION

Tau, α-synuclein, and prion protein's pathological behavior can shift from a non-pathological form into pathological conformations with higher aggregation potential. These pathological species can form oligomeric and fibrillar associations and interact with quality control systems, acting as seeds and ultimately contributing to progressive neuronal dysfunction [2, 3, 11, 14, 27].

Differences between them are also relevant: tau is heavily associated with the neuronal cytoskeleton, so loss of tau microtubule binding directly disrupts transport along the axon [16]. α-synuclein pathology is linked to presynaptic function, where it can disrupt movement of vesicles, transmission of impulses, and processes associated with the membrane [18, 19, 22]. Prion protein disease is unique due to its efficient conformational conversion and transmissibility [27, 29].

Keeping these differences aside, aggregation follows related methods: initial nucleation creates a seed, which promotes assembly; elongation recruits more monomers, while fragmentation of fibrils acts as new aggregation sites and causes secondary nucleation [13, 14, 47]. When enough pathogenic material accumulates, this process becomes self-amplifying, and different fibrillar conformations act as strains and preserve structural features as the template for later generations of aggregates [14, 47].

Tau and α-synuclein can move between cells and initiate aggregation in them. Introduction of pathogenic tau or α-synuclein experimentally can trigger additional endogenous aggregation, which acts as direct evidence for the spread via seeding [11, 14, 17, 35]. PrP follows the same logic and principle as a more extreme version, where its conformational propagation underlies the molecular basis of classical prion disease [27, 29].

A seed doesn't always act on identical molecules; for example, Tau and α-synuclein can influence aggregation of one and the other [11, 34, 35, 44]. Various strains of α-synuclein differ in their three-dimensional seed structure [11, 14]. In Parkinson's disease, tau protein has the function of boosting aggregation and transmission of α-Synuclein, another example of how neurodegenerative disorders may affect the spread of each other's pathology [11, 34, 35]. A patient may have multiple pathogenic protein species with the ability to alter each other's behavior [43, 44]. Interactions between tau and α-synuclein may explain the overlapping aspects of pathology in Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, and associated illnesses [11, 34, 35, 43]. According to this theory, disease phenotypes come from wider proteostatic environments where proteins, stress responses, and pathways of cells interact with each other [43].

Tau, α-synuclein, and PrP all place stress on protein clearance and quality control systems [7, 8]. Misfolded proteins interfere with these systems and the autophagy-lysosomal degradation pathway [7, 8]. They also interfere with mitochondrial activity, which can lead to oxidative stress and promote the aggregation of larger protofibrils that disrupt many synaptic and membrane-related functions [22, 23, 25]. Aggregates interfere with many synaptic and membrane-related functions, as discussed earlier; for instance, inflammatory mediators are released by microglia and astrocytes, which could influence the environment of neurons [24, 25, 36]. That is why common molecules that work via protein-specific biological mechanisms are associated with an

increased level of disease specificity. Knowing where each protein is located and its normal function can help researchers determine which systems are more likely to be damaged first. α-Synuclein is enriched in the functioning of the synapse, dopaminergic activity of neurons, and transport of vesicles to fuse with the presynaptic membrane [18, 19, 20]. Tau diseases damage and target microtubules and axonal transport, as the tau protein influences and regulates both these processes [16].

Pathological PrP has an extremely effective system of templated conformational conversion [27, 29]. Differences in the cell environment, strain, anatomical brain region, genetic influences, and protein interactions determine what the phenotype of the disease is or what clinical symptoms will be expressed after significant neuronal degradation [27, 32].

The total comparative analysis of each of the three neurodegenerative disorders shouldn't be taken solely as independent biological pathways but rather as recurrent sequences with different initial proteins. There is a sequence or structure of events corresponding to all three diseases; this framework is conformational instability, misfolding, nucleation, seeding, propagation, proteostasis disturbance, neuronal dysfunction, and degeneration of neurons [2, 3, 7, 11, 14, 27].

Table 2. Comparative features of tau, α-synuclein, and prion protein pathology.

Feature	Tau	α-Synuclein	Prion Protein
Main normal role	Microtubule stabilization, axonal preservation, and transport [1]	Neurotransmitter release and trafficking of synaptic vesicles [26, 27]	Normal PrP is involved in cellular processes, whereas conversion is characteristic of prion disease. [12]
Major disease association	AD and other tauopathies [11]	PD, DLB, MSA, and other synucleinopathies [9, 10, 13]	CJD and other prion diseases [12, 34]
Pathological transition	Abnormal PTMs, notably hyperphosphorylation , diminish microtubule binding and enhance aggregation [11].	Structurally flexible α-synuclein misfolds into oligomeric and fibrillar species [13, 28]	Templated conformational change of PrP^C to pathogenic PrP [12, 15]
Major aggregates	Oligomers, paired helical filaments, neurofibrillary tangles [15, 16]	Oligomers, fibrils, Lewy bodies, Lewy neurites, and cytoplasmic inclusions in glia [9, 10, 13, 20]	Pathological β-sheet-rich PrP aggregates [12, 15]
Seed-dependent aggregation	Yes [11, 24]	Yes [13, 14]	Yes [12, 15]
Cell-to-cell propagation	Prion-like [14, 25]	Prion-like [13, 14]	Classical prion propagation [12, 15]
Cross-seeding	Especially with α-synuclein and other proteins [13, 39, 40, 41]	Especially with tau and other proteins [13, 39, 40, 41]	Distinct classical prion conversion mechanism [12, 15]
Major cellular effects	Cytoskeletal instability, impaired axonal transport, synaptic dysfunction [11]	Synaptic, mitochondrial, membrane, and proteostasis dysfunction [21, 22, 30, 31]	Progressive neuronal dysfunction associated with self-propagating PrP conversion [12]
Natural infectious behavior	Not established as a	Not established as a	Yes, in transmissible prion

	classical infectious disease [14, 25]	classical infectious disease [13, 14]	disease [12, 34]

VII. THERAPEUTIC STRATEGIES AND EMERGING BIOMARKERS

Recent identifications of similarities in processes in tau, α-synuclein, and prion protein have changed the focus of therapeutic research from symptom management to disease treatment [3, 7]. As of today, the aim is to reshape the molecular mechanisms and pathways that lead to these diseases. Potential areas that could lead to ideas for interventions include synthesis, folding, post-translational modifications, oligomerization, fibril formation, cellular uptake, propagation, and causing degeneration in the pathogenic protein during the course of its life cycle [3, 7]. But the challenge still lies in choosing what is to be targeted and what would be optimal as a target, as monomers, oligomers, protofibrils, mature fibrils, and conformational strains all could produce very different consequences in relation to our biology [46, 47, 49].

One method of intervention could be to disrupt the mechanism early by reducing the availability or creation of aggregation-prone proteins [3, 7]. If we take the example of tau, this process could involve selectively targeting proteins with aberrant phosphorylation; we could also target proteins with pathogenic post-translational changes for α-synuclein and related proteins [3, 16].

The second method explored is the direct inhibition of aggregation; small compounds, in particular, can bind to monomeric or oligomeric species, disrupting the formation of beta-sheets and guiding proteins towards non-toxic assemblies [3, 7, 46, 47]. Two examples that have been examined are Anle138b and hydromethyltheonine; they have been developed as α-synuclein and tau aggregation inhibitors, respectively [37, 38]. Anle138b was developed as a modulator for oligomers and has strong experimental evidence involving α-synuclein and PrP aggregation [3, 37]. Hydromethyltheonine is a tau aggregation inhibitor that was evaluated clinically in Alzheimer's disease [38].

EGCG and other polyphenols additionally demonstrate anti-amyloidogenic effects in standard laboratory conditions, which impact α-synuclein and tau aggregation [2, 3]. Preclinical activity, however, is unable to always translate to clinical efficacy [3, 7].

Therefore, immunotherapy can act as an area for novel treatments and serves as a platform for active investigation [2, 3, 7]. Antibodies have been developed for different variations and species of tau; for example, antibodies have been generated against N-terminal regions, domains for microtubule interactions, phosphorylated epitopes, and various conformational pathologies of tau [2, 3]. One of the most significant issues is selectivity; medications and treatments must be directed only towards the pathological variants of a protein species to avoid disrupting the non-pathogenic variants of the same protein species and to maintain essential body functions [3, 7].

Treatment methods that enhance our biological protein clearance system or the activity of molecular chaperones may be a more holistic strategy for proteinopathies than focusing on the treatment of individual pathological proteins; some examples of possible treatments include heat shock response modulation, chaperone-guided therapies, and autophagy augmentation [6, 7, 39, 40]. Of course, there are some drawbacks to this process; for example, if degradation pathways are too active, they can impact cell activities that have no connection to pathological proteins [40]. Excessive or poorly targeted autophagy, particularly when lysosomal clearance is already impaired, can lead to autophagosome accumulation, degradation of essential cellular components, or additional neuronal stress [40]. In the same way, tau and α-synuclein are challenging to isolate without taking into account their normal neuronal roles [16, 18, 19].

Treatments in the future will probably depend on the selective targeting and identification of abnormal conformations rather than blindly decreasing all forms of a protein [3, 7, 46].

Neurodegenerative proteinopathies can lie dormant for years before clinical symptoms appear, creating an opportunity to modify the disease with treatments and increase their impact [1, 7].

Methods for seed amplification are also being

designed to identify and detect tau conformers and their activity rather than just the concentration of the protein [1, 2]. Differences may be relevant, as two patients with similar concentration levels of tau may have different amounts of pathological seeds that are biologically active in their bodies [1, 2]. Oligomeric species and post-translationally modified forms are being investigated as possible biomarkers for the detection of α-synuclein [1, 2, 3].

Both PMCA and RT-QuIC can increase the concentration of α-synuclein seeds from low amounts, and both have been used in CSF and peripheral tissues, for example, olfactory mucosa, gastrointestinal tissue, salivary glands, and skin [1, 2]. The mechanisms of seed amplification could inform researchers about the identity of α-synuclein strains, giving rise to the prospect of differentiating among various types of synucleinopathies rather than just identifying α-synuclein pathology [1, 2].

A lot of these strategies are based on the principle of prion disease; PMCA and RT-QuIC, for example, both multiply diseased seeds by providing non-pathological cellular protein substrates in settings optimal for template conversion [28, 29, 33].

Technologies are currently being developed with the purpose of increasing the rate of amplification, producing a larger quantity of enhanced seeds, and making them more efficient for transport [41, 42]. RT-FAST is a novel technology that uses nanopore/nanopore-based methods as both an amplification environment and a nanopore sensor to detect α-synuclein [41]. A model known as Nano-QuIC uses a different method. It employs nanoparticles to make amplification more efficient [42]. Such techniques are still being tested and developed, but they are indicators of a shift in the purpose of developing technologies [41, 42].

Approaches that we have today regarding biomarker detection are limited. CSF can have a high amount of disease-associated proteins, but their collection requires an invasive lumbar procedure. Although blood-based indicators are much simpler to gather, blood concentrations could be lower, and peripheral sources can distort interpretation [1, 2]. The seed amplifiers test can be lengthy to conduct on highly uniform recombinant-specific substrates. Various strains of the protein in question can also respond differently when tested under different conditions, which is another challenge in detection [1, 2, 28].

Biomarkers provide information about the presence of disease and what their dominant conformation could be, how strongly it seeds, and whether treatment is reducing its activity [1, 2, 33, 41, 42]. This kind of approach can push neurodegenerative medicine toward more accurate identification and classification of molecules, rather than relying on symptom-based approaches that come later in disease progression [1, 2].

VIII. FUTURE PERSPECTIVES

Studies regarding abnormal misfolding of proteins are moving away from the school of thought that neurodegenerative diseases are the result of singular protein deposits and are isolated conditions [2, 3, 43]. Tauopathies, synucleinopathies, and prion diseases may vary in their biology and structure, but they all have conformational instability, seeding, nucleation, strain production, propagation, and failure in proteostasis in common [2, 3, 7, 14]. For this reason future studies should not focus solely on single proteins but also on their cellular environment and the functions in which those proteins interact [43, 44].

Cross-seeding may grow to become an important aspect in the study of these diseases. Tau and α-synuclein can influence each other's aggregation [11, 34, 35]; interactions have also been reported among amyloid-beta, TDP-43, and other aggregation-prone proteins [43, 44].

Abnormalities in proteins can occur much before clinical neurodegeneration presents itself, and treatments may be too late if there is significant damage to the neurons [1, 7]. However, sensitivity must be compared against specificity, as pathogenic protein deposits or proteins may be found in patients who do not have any clinical neurodegeneration [1].

Neuronal and glial interactions can be studied on regulated and standardized platforms. These platforms are known as organoid models; within these platforms, structural techniques can be used for high-resolution assessment of oligomers and fibrils, alongside computational tools and large datasets to identify links between the primary amino acid sequence, native conformation of protein, clinical manifestation and disease phenotype, genetic background, and conformational pathological structure [45]. A question that may arise in the future is which pathogenic species should be treated and targeted. Targeting larger

fibrillar deposits may be ineffective, as soluble oligomers or seeds are often the toxic species [46, 47, 49]. However, inhibiting a stage of aggregation may redirect the pathway towards other soluble assemblies; this step makes it especially important to identify and determine whether treatment reduces or stabilizes potentially toxic oligomeric species [46, 47, 48]. To achieve effective treatment, more information about changes in monomers, oligomers, seeds, protofibrils, and mature fibrils throughout the span of the disease is necessary [7, 46, 49].

In the case of neurodegenerative diseases, combination therapy could be more useful than using only a specific treatment [3, 7]. Both treatments combined should limit pathogenic protein synthesis, reduce pathogenic aggregate formation, maintain proteostasis mechanisms, handle neuroinflammation, and inhibit extracellular aggregates; all of these mechanisms focus on different regions in the same disease network and target a variety of the specific proteins' pathological forms [3, 7, 36]. The main issue is that finding the correct combination of treatments for the specific disease proteinopathy, illness stage, and patient is difficult [3, 7].

IX. CONCLUSION

Considering that many neurodegenerative diseases share the accumulation of abnormal proteins, examination of tau, α-synuclein, and prion proteins suggests that protein misfolding is responsible for more than just protein accumulation [2, 3]. The conformational conversion in every system facilitates aggregation, produces physiologically active seeds, recruits more protein molecules, impairs cellular homeostasis, and leads to progressive neuronal degeneration [2, 7, 14].

Irregular post-translational modifications and aggregation of tau are linked to microtubule instability and abnormal axonal transport dysfunction [16]. Researchers also observe abnormal synapse function, mitochondrial stress, membrane disruption, and the development of neuronal or glial inclusions [18, 22, 23, 25]. α-synuclein disorder is associated with protein misfolding [2, 11, 20]. The prion protein is the most clear-cut example of templated conformational conversion, where diseased protein replicates its structure by binding to normal PrP [27, 29]. Though these proteins differ in many different factors, they act through similar processes that can be characterized by mechanisms such as seed-dependent amplification, proteostasis, oxidative damage and cellular responses, neural inflammation, and a long-term progression of pathology [2, 3, 7, 14, 27]. Evidence suggesting cross-seeding between tau and α-synuclein indicates that neurodegeneration is not always a single protein disorder and can involve the pathologies of proteins that accelerate each other's aggregation [11, 34, 35, 43, 44].

The aforementioned similarities between prion proteins, α-synuclein, and tau all provide vast opportunities for treatment and intervention based on inhibiting aggregation and seeding, strengthening the body's protein clearance system, selectively targeting aggregate-prone proteins, intracellular propagation, and other viable techniques [3, 7, 37, 39, 40].

REFERENCES

[1] Tregub PP, Kolotyeva NA, Chekulayev PA, Groshkov AA, Illarioshkin SN, Salmina AB, et al. Protein misfolding in the pathogenesis and diagnosis of neurodegenerative diseases. Sovrem Tekhnologii Med. 2025;17(4):60-77. doi:10.17691/stm2025.17.4.06.

[2] Wang JN, Dai LJ, Zhang ZT. Protein aggregation in neurodegenerative diseases. Chin Med J (Engl). 2025;138(21):2753-2768. doi:10.1097/CM9.0000000000003802.

[3] Sidoryk-Węgrzynowicz M, Adamiak K, Strużyńska L. Targeting protein misfolding and aggregation as a therapeutic perspective in neurodegenerative disorders. Int J Mol Sci. 2024;25(22):12448. doi:10.3390/ijms252212448.

[4] Brezic N, Gligorevic S, Sic A, Knezevic NN. Protein misfolding and aggregation as a mechanistic link between chronic pain and neurodegenerative diseases. Curr Issues Mol Biol. 2025;47(4):259. doi:10.3390/cimb47040259.

[5] Hartl FU, Hayer-Hartl M. Converging concepts of protein folding in vitro and in vivo. Nat Struct Mol Biol. 2009;16(6):574-581. doi:10.1038/nsmb.1591.

[6] Saibil H. Chaperone machines for protein folding, unfolding and disaggregation. Nat Rev Mol Cell Biol. 2013;14(10):630-642.

doi:10.1038/nrm3658.

[7] Sweeney P, Park H, Baumann M, Dunlop J, Frydman J, Kopito R, et al. Protein misfolding in neurodegenerative diseases: implications and strategies. Transl Neurodegener. 2017;6:6. doi:10.1186/s40035-017-0077-5.

[8] Lim J, Yue Z. Neuronal aggregates: formation, clearance, and spreading. Dev Cell. 2015;32(4):491-501. doi:10.1016/j.devcel.2015.02.002.

[9] Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc Natl Acad Sci U S A. 1998;95(11):6469-6473. doi:10.1073/pnas.95.11.6469.

[10] Tu PH, Galvin JE, Baba M, Giasson B, Tomita T, Leight S, et al. Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble alpha-synuclein. Ann Neurol. 1998;44(3):415-422. doi:10.1002/ana.410440324.

[11] Padilla-Godínez FJ, Vázquez-García ER, Trujillo-Villagrán MI, Soto-Rojas LO, Palomero-Rivero M, Hernández-González O, et al. α-Synuclein and tau: interactions, cross-seeding, and the redefinition of synucleinopathies as complex proteinopathies. Front Neurosci. 2025;19:1570553. doi:10.3389/fnins.2025.1570553.

[12] Dobson CM. Protein folding and misfolding. Nature. 2003;426(6968):884-890. doi:10.1038/nature02261.

[13] Törnquist M, Michaels TCT, Sanagavarapu K, Yang X, Meisl G, Cohen SIA, et al. Secondary nucleation in amyloid formation. Chem Commun (Camb). 2018;54(63):8667-8684. doi:10.1039/c8cc02204f.

[14] Jucker M, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature. 2013;501(7465):45-51. doi:10.1038/nature12481.

[15] Hasegawa M, Watanabe S, Kondo H, Akiyama H, Mann DMA, Saito Y, et al. 3R and 4R tau isoforms in paired helical filaments in Alzheimer's disease. Acta Neuropathol. 2014;127(2):303-305. doi:10.1007/s00401-013-1191-9.

[16] Guo T, Noble W, Hanger DP. Roles of tau protein in health and disease. Acta Neuropathol. 2017;133(5):665-704. doi:10.1007/s00401-017-1707-9.

[17] Vogel JW, Iturria-Medina Y, Strandberg OT, Smith R, Levitis E, Evans AC, et al. Spread of pathological tau proteins through communicating neurons in human Alzheimer's disease. Nat Commun. 2020;11(1):2612. doi:10.1038/s41467-020-15701-2.

[18] Sharma M, Burré J. α-Synuclein in synaptic function and dysfunction. Trends Neurosci. 2023;46(2):153-166. doi:10.1016/j.tins.2022.11.007.

[19] Burré J. The synaptic function of α-synuclein. J Parkinsons Dis. 2015;5(4):699-713. doi:10.3233/JPD-150642.

[20] Bennett MC. The role of alpha-synuclein in neurodegenerative diseases. Pharmacol Ther. 2005;105(3):311-331. doi:10.1016/j.pharmthera.2004.10.010.

[21] Horsager J, Borghammer P. Brain-first vs. body-first Parkinson's disease: an update on recent evidence. Parkinsonism Relat Disord. 2024;122:106101. doi:10.1016/j.parkreldis.2024.106101.

[22] Feng ST, Wang ZZ, Yuan YH, Sun HM, Chen NH, Zhang Y. Update on the association between alpha-synuclein and tau with mitochondrial dysfunction: implications for Parkinson's disease. Eur J Neurosci. 2021;53(9):2946-2959. doi:10.1111/ejn.14699.

[23] Risiglione P, Zinghirino F, Di Rosa MC, Magrì A, Messina A. Alpha-synuclein and mitochondrial dysfunction in Parkinson's disease: the emerging role of VDAC. Biomolecules. 2021;11(5):718. doi:10.3390/biom11050718.

[24] Béraud D, Hathaway HA, Trecki J, Chasovskikh S, Johnson DA, Johnson JA, et al. Microglial activation and antioxidant responses induced by the Parkinson's disease protein α-synuclein. J Neuroimmune Pharmacol. 2013;8(1):94-117. doi:10.1007/s11481-012-9401-0.

[25] Picca A, Guerra F, Calvani R, Romano R, Coelho-Júnior HJ, Bucci C, et al. Mitochondrial dysfunction, protein misfolding and neuroinflammation in Parkinson's disease: roads

to biomarker discovery. Biomolecules. 2021;11(10):1508. doi:10.3390/biom11101508.

[26] Pagano G, Taylor KI, Anzures Cabrera J, Simuni T, Marek K, Postuma RB, et al. Prasinezumab slows motor progression in rapidly progressing early-stage Parkinson's disease. Nat Med. 2024;30(4):1096-1103. doi:10.1038/s41591-024-02886-y.

[27] Hara H, Sakaguchi S. Virus infection, genetic mutations, and prion infection in prion protein conversion. Int J Mol Sci. 2021;22(22):12439. doi:10.3390/ijms222212439.

[28] Haley N. Amplification techniques for the detection of misfolded prion proteins in experimental and clinical samples. Curr Protoc Mol Biol. 2020;130(1):e118. doi:10.1002/cpmb.118.

[29] Saborio GP, Permanne B, Soto C. Sensitive detection of pathological prion protein by cyclic amplification of protein misfolding. Nature. 2001;411(6839):810-813. doi:10.1038/35081095.

[30] Makarava N, Savtchenko R, Baskakov IV. Methods of protein misfolding cyclic amplification. Methods Mol Biol. 2017;1658:169-183. doi:10.1007/978-1-4939-7244-9_13.

[31] Kim MO, Takada LT, Wong K, Forner SA, Geschwind MD. Genetic PrP prion diseases. Cold Spring Harb Perspect Biol. 2018;10(5):a033134. doi:10.1101/cshperspect.a033134.

[32] Mead S, Hermann P, Mok TH, Parchi P, Zerr I. Genetic causes and modifiers of prion diseases. Lancet Neurol. 2026;25(2):181-194. doi:10.1016/S1474-4422(25)00451-X.

[33] Green AJE. RT-QuIC: a new test for sporadic CJD. Pract Neurol. 2019;19(1):49-55. doi:10.1136/practneurol-2018-001935.

[34] Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. Science. 2003;300(5619):636-640. doi:10.1126/science.1082324.

[35] Williams T, Sorrentino Z, Weinrich M, Giasson BI, Chakrabarty P. Differential cross-seeding properties of tau and α-synuclein in mouse models of tauopathy and synucleinopathy. Brain Commun. 2020;2(2):fcaa090. doi:10.1093/braincomms/fcaa090.

[36] Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct Target Ther. 2023;8(1):359. doi:10.1038/s41392-023-01588-0.

[37] Wagner J, Ryazanov S, Leonov A, Levin J, Shi S, Schmidt F, et al. Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease. Acta Neuropathol. 2013;125(6):795-813. doi:10.1007/s00401-013-1114-9.

[38] Wischik CM, Bentham P, Gauthier S, Miller S, Kook K, Schelter BO. Oral tau aggregation inhibitor for Alzheimer's disease: design, progress and basis for selection of the 16 mg/day dose in a phase 3, randomized, placebo-controlled trial of hydromethylthionine mesylate. J Prev Alzheimers Dis. 2022;9(4):780-790. doi:10.14283/jpad.2022.63.

[39] Bose S, Cho J. Targeting chaperones, heat shock factor-1, and unfolded protein response: promising therapeutic approaches for neurodegenerative disorders. Ageing Res Rev. 2017;35:155-175. doi:10.1016/j.arr.2016.09.004.

[40] Krishnan S, Shrestha Y, Jayatunga DPW, Rea S, Martins R, Bharadwaj P. Activate or inhibit? Implications of autophagy modulation as a therapeutic strategy for Alzheimer's disease. Int J Mol Sci. 2020;21(18):6739. doi:10.3390/ijms21186739.

[41] Meyer N, Janot JM, Torrent J, Balme S. Real-time fast amyloid seeding and translocation of α-synuclein with a nanopipette. ACS Cent Sci. 2022;8(4):441-448. doi:10.1021/acscentsci.1c01404.

[42] Christenson PR, Li M, Rowden G, Larsen PA, Oh SH. Nanoparticle-enhanced RT-QuIC (Nano-QuIC) diagnostic assay for misfolded proteins. Nano Lett. 2023;23(9):4074-4081. doi:10.1021/acs.nanolett.3c01001.

[43] Spires-Jones TL, Attems J, Thal DR. Interactions of pathological proteins in neurodegenerative diseases. Acta Neuropathol. 2017;134(2):187-205. doi:10.1007/s00401-017-1709-7.

[44] Ren B, Zhang Y, Zhang M, Liu Y, Zhang D, Gong X, et al. Fundamentals of cross-seeding of amyloid proteins: an introduction. J Mater Chem

B. 2019;7(46):7267-7282. doi:10.1039/c9tb01871a.

[45] Shaikh S, Siddique L, Khalifey HT, Mahereen R, Raziq T, Firdous RM, et al. Brain organoid model systems of neurodegenerative diseases: recent progress and prospects. Front Neurosci. 2025;19:1604435. doi:10.3389/fnins.2025.1604435.

[46] Cascella R, Bigi A, Cremades N, Cecchi C. Effects of oligomer toxicity, fibril toxicity and fibril spreading in synucleinopathies. Cell Mol Life Sci. 2022;79(3):174. doi:10.1007/s00018-022-04166-9.

[47] Eisenberg D, Jucker M. The amyloid state of proteins in human diseases. Cell. 2012;148(6):1188-1203. doi:10.1016/j.cell.2012.02.022.

[48] Cappai R, Leck SL, Tew DJ, Williamson NA, Smith DP, Galatis D, et al. Dopamine promotes alpha-synuclein aggregation into SDS-resistant soluble oligomers via a distinct folding pathway. FASEB J. 2005;19(10):1377-1379. doi:10.1096/fj.04-3437fje.

[49] Siddiqi MK, Majid N, Malik S, Alam P, Khan RH. Amyloid oligomers, protofibrils and fibrils. Subcell Biochem. 2019;93:471-503. doi:10.1007/978-3-030-28151-9_16.