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CONVERGENT MECHANISMS AND NOVEL THERAPEUTIC HORIZONS IN NEURODEGENERATIVE DISEASES: A COMPREHENSIVE REVIEW

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ABSTRACT

Neurodegenerative diseases (NDDs) represent one of the most pressing medical, social, and economic challenges of the twenty-first century. Characterized by the progressive structural and functional loss of neurons within the central and peripheral nervous systems, conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD) share striking mechanistic overlaps despite their distinct clinical phenotypes. Historically categorized and managed as isolated clinical entities, recent breakthroughs in molecular biology, neuroimaging, and genetics have revealed a highly convergent pathophysiological landscape. Central to this shared pathogenesis are protein misfolding and aggregation, mitochondrial dysfunction, bioenergetic failure, chronic neuroinflammation, impairment of proteostatic networks, glutamate-mediated excitotoxicity, and non-cell-autonomous mechanisms involving glial interactions. This review provides a comprehensive synthesis of the shared molecular pathways driving neurodegeneration, contrasts these against disease-specific pathobiological profiles, evaluates the modern landscape of diagnostic fluid and imaging biomarkers, and critically analyzes the shift from symptomatic management to disease-modifying therapies. Specifically, we dissect emerging therapeutic modalities, including antisense oligonucleotides, adeno-associated virus-mediated gene therapies, monoclonal antibodies against pathological protein conformers, small-molecule modulators of neuroinflammation, and cellular reprogramming strategies. Finally, we discuss current translational hurdles—such as blood–brain barrier penetrance, patient stratification, and trial design—and propose an integrative framework for future therapeutic intervention.

Keywords: Neurodegeneration, Protein Misfolding, Proteostasis, Neuroinflammation, Mitochondrial Dysfunction, Gene Therapy, Biomarkers, Disease-Modifying Therapeutics.

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1. Introduction

Neurodegenerative diseases represent a heterogeneous group of chronic, progressive disorders characterized by the selective, gradual loss of vulnerable neuronal populations in the central nervous system. Driven by unprecedented global population aging, the socio-economic impact of neurodegenerative conditions has reached crisis levels (1). According to global epidemiological estimates, over 55 million individuals currently live with dementia worldwide, a number projected to exceed 139 million by 2050. The global direct and indirect healthcare expenditures for dementia alone exceed USD $1.3 trillion annually, while conditions like Parkinson's disease show the fastest-growing prevalence among neurological movement disorders (2).

Major neurodegenerative diseases covered in this synthesis account for the overwhelming majority of cases globally. Alzheimer's disease is the primary cause of dementia, characterized by progressive short-term memory impairment and executive dysfunction. Parkinson's disease is defined by nigrostriatal dopaminergic cell loss leading to bradykinesia, resting tremor, and rigidity (3). Huntington's disease is an autosomal dominant monogenic disorder leading to striatal medium spiny neuron degeneration, presenting with chorea, cognitive decline, and psychiatric symptoms (4). Amyotrophic lateral sclerosis is a fatal motor neuron disease marked by rapid degeneration of upper and lower motor neurons, causing muscle atrophy, paralysis, and respiratory failure (5). Frontotemporal dementia involves primary focal degeneration of the frontal and temporal lobes, driving profound alterations in social behaviour, personality, and executive language skills (6).

For decades, neurodegenerative research operated within rigid disease-specific silos. However, clinical drug trial failures, widespread discovery of mixed pathology in aged brains, and advances in single-cell transcriptomics have catalysed a paradigm shift. This review provides a timely, integrative synthesis of convergent pathobiological cascades across AD, PD, HD, ALS, and FTD. By examining shared mechanistic drivers—including protein aggregation kinetics, mitochondrial collapse, glial activation, and impaired proteostasis—we evaluate how emerging biomarkers and targeted therapies are moving the field from purely symptomatic management toward true disease modification (7,8).

2. Common Pathological Mechanisms

The structural destabilization and misfolding of native proteins represent a central hallmark of neurodegeneration. Under physiological conditions, proteins adopt native three-dimensional conformations

required for biological functionality. In disease states, genetic mutations, post-translational modifications, or environmental stress cause proteins to expose hydrophobic domains, inducing misfolding (9). Misfolded monomers self-assemble through an energy-favourable pathway, progressing from soluble monomeric states to low-molecular-weight oligomers, protofibrils, and insoluble fibrillar aggregates. Soluble oligomers represent the primary neurotoxic entities, disrupting lipid bilayers, forming non-specific membrane pores, impairing ion homeostasis, and sequestering essential functional cellular proteins (10).

Neurons rely almost exclusively on mitochondrial oxidative phosphorylation to generate ATP for maintaining membrane potentials, neurotransmitter synthesis, and synaptic transmission. Mitochondrial decay is a shared feature across the neurodegenerative spectrum. Impairment of electron transport chain complexes reduces ATP synthesis and elevates the leakage of reactive oxygen species (ROS) (11). Uncontrolled ROS production oxidizes cellular lipids, proteins, and nucleic acids, initiating structural loss and intrinsic apoptotic cascades. Furthermore, selective mitophagy deficits prevent the clearance of damaged, depolarized mitochondria, leading to persistent intracellular oxidative distress and permeability transition pore opening (11,12).

While transient neuroinflammatory responses serve a neuroprotective role in clearing debris, chronic neuroinflammation acts as an active driver of neurodegenerative progression. Microglia transition from a homeostatic state to a Disease-Associated Microglia (DAM) phenotype upon recognizing Damage-Associated Molecular Patterns via pattern recognition receptors. Activated microglia secrete elevated levels of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6), which induce direct neurotoxicity and convert resting astrocytes into neurotoxic A1 reactive astrocytes. Reactive astrocytes lose their essential homeostatic capabilities, including glutamate reuptake and neurotrophic factor secretion, further exacerbating neuronal damage (9,9,11).

Cellular proteostasis is maintained through a coordinated network of molecular chaperones, the Ubiquitin-Proteasome System (UPS), and the Autophagy-Lysosomal Pathway (ALP). Age-dependent and disease-specific burdens lead to the breakdown of these clearance systems. Intracellular aggregates directly block the proteasomal catalytic core, preventing the routine turnover of short-lived regulatory proteins. Concurrently, lysosomal acidification deficits, impaired autophagosome-lysosome fusion, and genetic mutations in lysosomal enzymes impair autophagic flux, allowing large

pathological protein aggregates and damaged organelles to accumulate uncontrollably (13).

Excitotoxicity occurs when excess extracellular glutamate overstimulates postsynaptic ionotropic glutamate receptors, specifically NMDA and AMPA receptors. This overstimulation causes an uncontrolled influx of extracellular calcium into the postsynaptic neuron. Intracellular calcium overload hyperactivates destructive enzymatic pathways, including calpains, caspases, phospholipases, and neuronal nitric oxide synthase. Excessive calcium uptake into the mitochondrial matrix disrupts membrane potential and unleashes apoptotic signaling, aggravated by impaired astrocytic glutamate reuptake (14).

Synaptic loss is the strongest structural correlate of cognitive and motor decline in neurodegenerative diseases, occurring long before overt neuronal cell death. Soluble pathological protein oligomers localize directly to pre- and post-synaptic compartments. Presynaptically, oligomers disrupt synaptic vesicle docking and neurotransmitter release. Postsynaptically, pathological proteins drive the endocytosis and loss of AMPA and NMDA receptors, causing dendritic spine loss and collapse of long-term potentiation. Additionally, inappropriate reactivation of the classical complement cascade tags functional synapses for microglial phagocytosis, driving premature circuit disassembly (11,15).

Neurodegenerative diseases spread stereotypically across interconnected neural networks through a prion-like mechanism involving non-cell-autonomous cell-to-cell transfer of misfolded protein seeds. Pathogenic protein conformers serve as templates that induce conformational misfolding in native endogenous proteins. Internalized seeds are released into the extracellular space via exocytosis, exosomes, or direct cell-to-cell connections. Neighbouring or synaptically connected neurons internalize these seeds through endocytosis, initiating new waves of protein misfolding and driving predictable anatomical disease staging (16,17).

3. Disease-Specific Sections

Alzheimer's Disease

Alzheimer's disease accounts for 60–80% of all dementia cases globally, presenting insidiously with early episodic memory loss, executive dysfunction, and spatial disorientation. The defining neuropathology includes extracellular amyloid-beta plaques derived from sequential cleavage of APP by β- and γ-secretases, and intracellular neurofibrillary tangles composed of hyperphosphorylated tau (18). Cholinergic neurons of the basal forebrain and pyramidal neurons of the entorhinal cortex and hippocampus exhibit selective vulnerability.

According to the amyloid cascade hypothesis, aberrant amyloid-beta accumulation initiates downstream tau hyperphosphorylation, microglial activation, synaptic loss, and widespread neurodegeneration (19).

Parkinson's Disease

Parkinson's disease affects 1–2% of the population over age 60, characterized by cardinal motor signs including bradykinesia, resting tremor, rigidity, and postural instability. These motor features are preceded by non-motor prodromal manifestations such as hyposmia, REM sleep behaviour disorder, and severe constipation. Pathologically, PD is defined by the selective loss of dopaminergic neurons in the substantia nigra pars compacta and intracellular inclusions known as Lewy bodies, composed primarily of misfolded α-synuclein. Mountingly, evidence points to the gut-brain axis as an initiation site where α-synuclein misfolds in the enteric nervous system and propagates to the brainstem via the vagus nerve (20).

Huntington's Disease

Huntington's disease is an autosomal dominant disorder with a typical onset between 30 and 50 years of age, presenting with choreiform involuntary movements, progressive cognitive decay, and prominent affective disturbances. The condition is caused by a CAG trinucleotide repeat expansion in Exon 1 of the HTT gene, encoding an expanded polyglutamine tract in the huntingtin protein. Polyglutamine expansion confers a toxic gain-of-function to mutant huntingtin, causing nuclear translocation of toxic N-terminal fragments, transcriptional dysregulation, impaired axonal transport, mitochondrial toxicity, and selective degeneration of GABAergic medium spiny neurons in the striatum (21).

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis has an annual incidence of approximately 2 to 3 per 100,000, typically presenting in the fifth or sixth decade with progressive muscle weakness, atrophy, and fasciculations, leading to death from respiratory failure within 3 to 5 years. Pathology targets upper motor neurons in the primary motor cortex and lower motor neurons in the brainstem and ventral horn of the spinal cord. Over 97% of sporadic cases feature pathological cytoplasmic clearing and aggregation of TDP-43, causing toxic loss of nuclear RNA-splicing function paired with cytoplasmic gain-of-toxicity and neuroinflammatory motor unit decline (22).

Other Neurodegenerative Conditions

Frontotemporal dementia comprises a spectrum of non-Alzheimer dementias characterized by behavioural alterations, disinhibition, or primary progressive aphasias, driven pathologically by frontotemporal lobar degeneration with tau,

TDP-43, or FUS inclusions. Dementia with Lewy bodies presents with cognitive fluctuations, recurrent visual hallucinations, and spontaneous parkinsonism, driven by widespread neocortical and subcortical Lewy body pathology. Multiple system atrophy is an aggressive synucleinopathy distinguished by pathological α-synuclein accumulation within oligodendrocytes as Glial Cytoplasmic Inclusions, causing autonomic failure, cerebellar ataxia, and parkinsonism (23).

Comparison of Major Neurodegenerative Diseases

4. Genetic and Environmental Risk Factors

Monogenic forms account for less than 10 to 15% of total neurodegenerative disease cases but offer critical insights into biological pathways. Autosomal dominant mutations in APP, PSEN1, and PSEN2 drive early-onset familial AD by altering secretase processing to favor toxic amyloid-beta 42. Trinucleotide repeat expansions in HTT determine Huntington's disease, while hexanucleotide repeat expansions in C9orf72 represent the leading genetic cause of both familial ALS and FTD. Mutations in SOD1, TARDBP, and FUS drive distinct familial ALS phenotypes, whereas recessive mutations in PRKN, PINK1, and DJ-1 cause early-onset parkinsonism (24).

The vast majority of neurodegenerative cases are sporadic, arising from a complex polygenic architecture combined with low- or moderate-penetrance risk variants. The APOE ε4 allele represents the strongest genetic risk factor for sporadic AD, increasing risk threefold in heterozygotes and up to twelvefold in homozygotes. Rare loss-of-function variants in TREM2 impair microglial activation around plaques and elevate AD risk. Heterozygous mutations in GBA1 impair lysosomal glucocerebrosidase activity, representing the single greatest genetic risk factor for sporadic Parkinson's disease, while variants in LRRK2 modulate autophagy and kinase activity (25).

Aging represents the single greatest non-genetic risk factor across all major neurodegenerative diseases, characterized by cellular senescence, genomic instability, epigenetic alterations, and a progressive decline in proteostatic capacity. Prolonged environmental exposures to organochlorine pesticides, herbicides like paraquat, and industrial solvents elevate PD risk through mitochondrial Complex I inhibition and oxidative stress. Repetitive traumatic brain injury induces chronic traumatic encephalopathy characterized by perivascular tau deposition and accelerated microglial activation. Furthermore, midlife cardiovascular risk factors, systemic low-grade inflammation, and gut microbiome dysbiosis alter intestinal permeability and

promote chronic central neuroinflammation (26).

5. Diagnosis and Biomarkers

The diagnostic landscape for neurodegenerative disorders has undergone a major shift from post-mortem pathology confirmation to in vivo biological framework definitions utilizing fluid and imaging biomarkers. Ultra-sensitive assay platforms like Single Molecule Array (Simoa) now enable accurate quantification of central biomarkers directly from peripheral blood plasma. Plasma p-tau217 and p-tau181 exhibit high diagnostic accuracy for Alzheimer's pathology prior to overt clinical symptoms. Reductions in plasma or CSF Aβ42/Aβ40 ratios reflect extracellular amyloid sequestration into parenchymal plaques (24).

Neurofilament light chain (NfL) serves as a sensitive, dynamic marker of neuroaxonal breakdown and axonal injury, showing marked elevations across ALS, FTD, and active AD. Glial fibrillary acidic protein (GFAP) provides a sensitive blood-based measure of reactive astrogliosis. In synucleinopathies, Seed Amplification Assays (such as RT-QuIC) leverage protein amplification to detect femtomolar concentrations of misfolded, seeding-competent α-synuclein in CSF or skin biopsies with near 100% specificity, revolutionizing early diagnosis for PD and DLB (26).

Advanced molecular neuroimaging provides crucial spatial mapping of pathological features in the living brain. Positron Emission Tomography (PET) radiotracers targeting amyloid-beta and tau quantify cortical plaque burden and neurofibrillary tangle distribution, tracking closely with clinical dementia severity. Dopamine transporter (DaTscan) SPECT visualizes presynaptic dopamine terminal loss in the striatum to differentiate parkinsonian syndromes from essential tremor. Quantitative structural MRI measures regional atrophy patterns, such as hippocampal loss in AD or frontotemporal lobar loss in FTD, while DTI detects white matter tract degradation (25).

6. Current Therapies

Standard symptomatic therapies offer transient functional relief without altering the underlying rate of neurodegenerative cell death. In Alzheimer's disease, cholinesterase inhibitors (donepezil, rivastigmine, galantamine) temporarily elevate synaptic acetylcholine levels to support cognitive function, while memantine blocks excessive NMDA receptor excitotoxicity. In Parkinson's disease, levodopa combined with carbidopa remains the gold standard for restoring motor function, supported by dopamine agonists and MAO-B inhibitors. In

ALS, riluzole inhibits presynaptic glutamate release to extend survival modestly, while edaravone acts as a free radical scavenger to reduce oxidative stress (27).

The approval of human monoclonal antibodies targeting aggregated forms of amyloid-beta—including Lecanemab and Donanemab—marks a major milestone in disease-modifying therapy for Alzheimer's disease. These engineered antibodies target distinct species along the amyloid pathway, such as soluble protofibrils or mature plaque core amyloid, recruiting microglial Fc-receptors to drive phagocytic plaque clearance. Phase 3 clinical trials demonstrated robust amyloid plaque clearance accompanied by a 27 to 35% slowing of cognitive and functional decline over 18 months. However, their administration requires monitoring for Amyloid-Related Imaging Abnormalities, including cerebral edema (ARIA-E) and microhemorrhages (ARIA-H), which occur more frequently in APOE ε4 carriers (28).

Non-pharmacological strategies provide crucial synergistic benefits by enhancing brain resilience and neuroplasticity. Regular aerobic exercise stimulates the expression of Brain-Derived Neurotrophic Factor (BDNF), promotes synaptic plasticity, and improves cerebral perfusion. Cognitive engagement and structured cognitive training strengthen network connectivity. Furthermore, adhering to anti-inflammatory, nutrient-dense dietary patterns—such as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet—reduces systemic metabolic stress and slows cognitive decline in vulnerable older adults (29).

7. Emerging and Future Therapeutic Strategies

Targeted gene therapies and nucleic acid medicines represent a rapidly expanding therapeutic frontier. Antisense oligonucleotides (ASOs) are single-stranded synthetic sequence-specific molecules designed to bind target pre-mRNA, inducing degradation or correcting aberrant splicing. Tofersen is an approved ASO that selectively degrades SOD1 mRNA in familial ALS, lowering neurofilament light chain levels and stabilizing motor function. ASOs targeting HTT mRNA for Huntington's disease, as well as splicing modulators designed to restore STMN2 and UNC13A expression following TDP-43 loss in ALS/FTD, are in active clinical development. Additionally, AAV-mediated gene therapies are being evaluated for gene replacement and CRISPR-based gene editing (30).

Targeted protein degradation technologies offer a unique mechanism to eliminate pathogenic intracellular proteins. Proteolysis-Targeting Chimeras (PROTACs) are bifunctional small molecules that simultaneously bind a target pathological

protein and recruit an E3 ubiquitin ligase. This forced proximity induces polyubiquitination and proteasomal degradation of misfolded tau, α-synuclein, or mutant huntingtin. Emerging AUTAC and LYTAC platforms expand these degradation capabilities to the autophagy-lysosomal network, enabling the clearance of large insoluble intracellular inclusions and extracellular aggregations (31).

Next-generation immunotherapies extend beyond extracellular antibody clearing toward intracellular neutralization. Adeno-associated virus vectors are being engineered to deliver intracellular antibodies, known as intrabodies, directly into the neuronal cytoplasm. These single-chain variable fragments bind misfolded tau, α-synuclein, or mutant huntingtin within the cell, neutralizing toxic seeds and preventing template propagation without triggering inflammatory cascades. Concurrently, bispecific antibodies engineered with transferrin receptor shuttles enhance blood–brain barrier crossing via receptor-mediated transcytosis (32).

Modulating neuroinflammation represents a high-potential, non-protein-centric approach to neuroprotection. Small-molecule inhibitors targeting the NLRP3 inflammasome prevent microglial assembly and suppress the release of pro-inflammatory IL-1β and IL-18. Agonistic monoclonal antibodies targeting microglial TREM2 promote microglial survival, energetic efficiency, and protective compaction around toxic amyloid deposits. Furthermore, blocking classical complement component C1q prevents inappropriate microglial phagocytosis of functional synapses, preserving neural network integrity (33).

Cellular reprogramming and regenerative medicine aim to replace lost neuronal subpopulations and restore damaged neural circuits. Transplantation of autologous or HLA-matched induced pluripotent stem cell (iPSC)-derived dopaminergic progenitor cells into the striatum of Parkinson's patients has advanced to clinical trials, demonstrating graft survival and functional integration. Additionally, direct in vivo lineage reprogramming approaches utilize viral vector delivery of specific transcription factors to convert resident striatal or cortical astrocytes directly into functional, subtype-specific neurons in situ (34).

8. Challenges and Limitations

Translating preclinical successes into successful clinical disease-modifying therapies faces major biological and practical obstacles. The blood–brain barrier (BBB) forms a strict physical and biochemical barrier enforced by tight junctions, pericytes, and astrocytic end-feet. Over 98% of small-molecule drugs and virtually all large biotherapeutics fail to achieve therapeutic

concentrations in the brain parenchyma following systemic administration. Overcoming this limitation requires advanced delivery technologies, such as receptor-mediated transcytosis shuttles or focused ultrasound paired with microbubbles to transiently open tight junctions (35).

Phenotypic and molecular heterogeneity within patient populations creates significant hurdles for clinical trials. Clinical spectrums categorized under single disease names encompass distinct molecular sub-phenotypes driven by varying combinations of genetic risk factors, cellular pathway deficits, and environmental influences. Furthermore, post-mortem analyses reveal that aged brains rarely exhibit isolated protein pathologies, with up to 50% of late-onset AD brains presenting with co-occurring Lewy bodies or TDP-43 pathology. Enrolling heterogeneous patient cohorts without precise biomarker stratification dilutes therapeutic treatment signals (36).

The timing of therapeutic intervention remains a critical factor in clinical trial outcomes. Extensive neuroaxonal loss, synaptic clearance, and circuit disassembly occur decades prior to the manifestation of overt clinical symptoms. Initiating disease-modifying therapies during moderate-to-severe clinical stages, when neural architecture is already depleted, is unlikely to restore lost cognitive or motor function. Transitioning clinical trial designs toward secondary and primary prevention in asymptomatic, biomarker-positive individuals represents a vital priority (37).

Transgenic animal models present severe limitations in recapitulating human neurodegenerative pathology. Standard rodent models typically rely on the overexpression of rare human genetic mutations, successfully mimicking specific protein aggregation features but failing to capture the complex, age-dependent, non-cell-autonomous mechanisms and cortical complexity of human brains. Developing human iPSC-derived 3D cerebral organoids, microfluidic brain-on-a-chip systems, and humanized animal models is essential to improve translational predictability (38).

9. Future Perspectives and Conclusion

The future of neurodegenerative disease management lies in personalized, combination-based precision medicine. Given that neurodegeneration involves multiple converging, self-amplifying pathological cascades, single-target monotherapies are unlikely to fully halt disease progression. Future clinical regimens will combine protein-clearing modalities with neuroprotective small molecules, NLRP3 inflammasome inhibitors, and mitochondrial enhancers. Widespread screening using sensitive blood biomarkers will enable early detection in middle age,

while adaptive platform trial designs will allow simultaneous evaluation of multiple pipeline agents (39).

Neurodegenerative diseases represent complex, multi-system disorders driven by shared molecular cascades, including protein misfolding, proteostatic failure, mitochondrial decay, and chronic neuroinflammation. The field has achieved a fundamental transformation, progressing from descriptive clinical classification toward an objective, biomarker-driven molecular classification. With the clinical validation of amyloid-clearing monoclonal antibodies and gene-silencing therapies, targeted modification of neurodegenerative processes has become a reality. By addressing blood–brain barrier delivery, refining stratification via fluid and imaging biomarkers, and implementing early multi-target combination therapies, the scientific community is moving closer to transforming these once-untreatable conditions into manageable or preventable health states (40).

REFERENCES

1. Tesco G, Lomoio S. Pathophysiology of neurodegenerative diseases: An interplay among axonal transport failure, oxidative stress, and inflammation? Seminars in Immunology. 2022 Jan;59:101628. doi:10.1016/j.smim.2022.101628
2. Li Y, Jönsson L. The health and economic burden of brain disorders: Consequences for investment in diagnosis, treatment, prevention and R&D. Cerebral Circulation - Cognition and Behavior. 2025;8:100377. doi:10.1016/j.cccb.2025.100377
3. Tanaka M. Parkinson's Disease: Bridging Gaps, Building Biomarkers, and Reimagining Clinical Translation [Internet]. Medicine and Pharmacology; 2025 [cited 2026 Oct 6]. Available from: https://www.preprints.org/manuscript/202506.2099/v2 doi:10.20944/preprints202506.2099.v2
4. Ehrlich ME. Huntington's Disease and the Striatal Medium Spiny Neuron: Cell-Autonomous and Non-Cell-Autonomous Mechanisms of Disease. Neurotherapeutics. 2012 Apr;9(2):270–84. doi:10.1007/s13311-012-0112-2
5. Perry J, Pratt, Getzoff. Amyotrophic lateral sclerosis: update and new developments. DNND. 2012 Feb;1. doi:10.2147/DNND.S19803
6. Young JJ, Lavakumar M, Tampi D, Balachandran S, Tampi RR. Frontotemporal dementia: latest evidence and clinical implications. Therapeutic Advances in Psychopharmacology. 2018 Jan;8(1):33–48. doi:10.1177/2045125317739818
7. Hussain R, Zubair H, Pursell S, Shahab M. Neurodegenerative Diseases: Regenerative Mechanisms and Novel Therapeutic Approaches. Brain Sciences. 2018 Sep 15;8(9):177. doi:10.3390/brainsci8090177
8. 15th Conference Clinical Trials Alzheimer's Disease, November 29–December 2, 2022, San Francisco, CA, USA: Posters (Clinical Trial Alzheimer's Disease). The Journal of Prevention of Alzheimer's Disease. 2022 Dec;9:51–248. doi:10.14283/jpad.2022.97
9. Guo L, Tian J, Du H. Mitochondrial Dysfunction and Synaptic Transmission Failure in Alzheimer's Disease. Journal of Alzheimer's Disease. 2017 Apr 19;57(4):1071–86. doi:10.3233/JAD-160702

10. 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 Dec;6(1):6. doi:10.1186/s40035-017-0077-5

11. Li A, Gao M, Liu B, Qin Y, Chen L, Liu H, et al. Mitochondrial autophagy: molecular mechanisms and implications for cardiovascular disease. Cell Death Dis. 2022 May 9;13(5):444. doi:10.1038/s41419-022-04906-6

12. Rinauro DJ, Chiti F, Vendruscolo M, Limbocker R. Misfolded protein oligomers: mechanisms of formation, cytotoxic effects, and pharmacological approaches against protein misfolding diseases. Mol Neurodegeneration. 2024 Feb 20;19(1):20. doi:10.1186/s13024-023-00651-2

13. Du M, Yu Y, Wang J, Ji C. Autophagy–Lysosome Pathway Dysfunction in Neurodegeneration and Cancer: Mechanisms and Therapeutic Opportunities. IJMS. 2025 Dec 29;27(1):366. doi:10.3390/ijms27010366

14. Shukla M, Narayan M. Proteostasis and Its Role in Disease Development. Cell Biochem Biophys. 2024 Oct 18;83(2):1725–41. doi:10.1007/s12013-024-01581-6

15. Subramanian J, Savage JC, Tremblay MÈ. Synaptic Loss in Alzheimer's Disease: Mechanistic Insights Provided by Two-Photon in vivo Imaging of Transgenic Mouse Models. Front Cell Neurosci. 2020 Dec 17;14:592607. doi:10.3389/fncel.2020.592607

16. Chen B, Chen T, Sun Z, Liu L, Jia Y, Ji Y, et al. The aggregation of amyloid-β: from condensation, nucleation, and conformation to targeting therapy. Life Sciences. 2026 Jul;396:124397. doi:10.1016/j.lfs.2026.124397

17. Wu W long, Gong X xi, Qin Z hong, Wang Y. Molecular mechanisms of excitotoxicity and their relevance to the pathogenesis of neurodegenerative diseases—an update. Acta Pharmacol Sin. 2025 Dec;46(12):3129–42. doi:10.1038/s41401-025-01576-w

18. Ballinger EC, Ananth M, Talmage DA, Role LW. Basal Forebrain Cholinergic Circuits and Signaling in Cognition and Cognitive Decline. Neuron. 2016 Sep;91(6):1199–218. doi:10.1016/j.neuron.2016.09.006

19. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegeneration. 2019 Dec;14(1):32. doi:10.1186/s13024-019-0333-5

20. Váradi C. Clinical Features of Parkinson's Disease: The Evolution of Critical Symptoms. Biology. 2020 May 19;9(5):103. doi:10.3390/biology9050103

21. Roos RA. Huntington's disease: a clinical review. Orphanet J Rare Dis. 2010 Dec;5(1):40. doi:10.1186/1750-1172-5-40

22. Mead RJ, Shan N, Reiser HJ, Marshall F, Shaw PJ. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nat Rev Drug Discov. 2023 Mar;22(3):185–212. doi:10.1038/s41573-022-00612-2

23. Antonioni A, Raho EM, Lopriore P, Pace AP, Latino RR, Assogna M, et al. Frontotemporal Dementia, Where Do We Stand? A Narrative Review. IJMS. 2023 Jul 21;24(14):11732. doi:10.3390/ijms241411732

24. Bekris LM, Yu CE, Bird TD, Tsuang DW. Review Article: Genetics of Alzheimer Disease. J Geriatr Psychiatry Neurol. 2010 Dec;23(4):213–27. doi:10.1177/0891988710383571

25. Ebenau JL, Van Der Lee SJ, Hulsman M, Tesi N, Jansen IE, Verberk IMW, et al. Risk of dementia in APOE ε4 carriers is mitigated by

a polygenic risk score. Alz & Dem Diag Ass & Dis Mo. 2021 Jan;13(1):e12229. doi:10.1002/dad2.12229

26. Kritsilis M, V. Rizou S, Koutsoudaki PN, Evangelou K, Gorgoulis VG, Papadopoulos D. Ageing, Cellular Senescence and Neurodegenerative Disease. IJMS. 2018 Sep 27;19(10):2937. doi:10.3390/ijms19102937
27. Grossberg GT. Cholinesterase Inhibitors for the Treatment of Alzheimer's Disease: Current Therapeutic Research. 2003 Apr;64(4):216–35. doi:10.1016/S0011-393X(03)00059-6
28. Romero Garavito A, Díaz Martínez V, Juárez Cortés E, Negrete Díaz JV, Montilla Rodríguez LM. Impact of physical exercise on the regulation of brain-derived neurotrophic factor in people with neurodegenerative diseases. Front Neurol. 2025 Jan 28;15:1505879. doi:10.3389/fneur.2024.1505879
29. Alkhalifa AE, Al Mokhlf A, Ali H, Al-Ghraiybah NF, Syropoulou V. Anti-Amyloid Monoclonal Antibodies for Alzheimer's Disease: Evidence, ARIA Risk, and Precision Patient Selection. JPM. 2025 Sep 15;15(9):437. doi:10.3390/jpm15090437
30. Collotta D, Bertocchi I, Chiapello E, Collino M. Antisense oligonucleotides: a novel Frontier in pharmacological strategy. Front Pharmacol. 2023 Nov 17;14:1304342. doi:10.3389/fphar.2023.1304342
31. Bazzacco A, Mercorelli B, Loregian A. PROteolysis TArgeting Chimeras (PROTACs) and beyond: targeted degradation as a new path to fight microbial pathogens. Münz C, editor. FEMS Microbiology Reviews. 2025 Jan 14;49:fuaf046. doi:10.1093/femsre/fuaf046
32. Böldicke T. Therapeutic Potential of Intrabodies for Cancer Immunotherapy: Current Status and Future Directions. Antibodies. 2022 Jul 18;11(3):49. doi:10.3390/antib11030049
33. Sharma B, Satija G, Madan A, Garg M, Alam MM, Shaquiquzzaman M, et al. Role of NLRP3 Inflammasome and Its Inhibitors as Emerging Therapeutic Drug Candidate for Alzheimer's Disease: a Review of Mechanism of Activation, Regulation, and Inhibition. Inflammation. 2023 Feb;46(1):56–87. doi:10.1007/s10753-022-01730-0
34. Peng J, Zeng X. The role of induced pluripotent stem cells in regenerative medicine: neurodegenerative diseases. Stem Cell Res Ther. 2011 Aug;2(4):32. doi:10.1186/scrt73
35. He Y, Qu M, Yu L, He L, Lu Y, Hong J, et al. Blood–Brain Barrier: Structure, Function, Diseases, and Drug Delivery Systems. MedComm. 2026 Apr;7(4):e70712. doi:10.1002/mco2.70712
36. Sun YH, Wu YL, Liao BY. Phenotypic heterogeneity in human genetic diseases: ultrasensitivity-mediated threshold effects as a unifying molecular mechanism. J Biomed Sci. 2023 Jul 31;30(1):58. doi:10.1186/s12929-023-00959-7
37. Velázquez De Castro-Bono A, Castro-Luna G, Guil-Guerrero JL. Beyond the Amyloid Hypothesis: Systemic Drivers, CNS-PNS Crosstalk, and the Future of Alzheimer's Disease Therapeutics. IJMS. 2026 Jun 2;27(11):5042. doi:10.3390/ijms27115042
38. Harvey BK, Richie CT, Hoffer BJ, Airavaara M. Transgenic animal models of neurodegeneration based on human genetic studies. J Neural Transm. 2011 Jan;118(1):27–45. doi:10.1007/s00702-010-0476-6
39. Arafah A, Khatoon S, Rasool I, Khan A, Rather MA, Abujabal KA, et al. The Future of Precision Medicine in the Cure of

Alzheimer's Disease. Biomedicines. 2023 Jan 25;11(2):335. doi:10.3390/biomedicines11020335

40. Sheikh S, Safia, Haque E, Mir SS. Neurodegenerative Diseases: Multifactorial Conformational Diseases and Their Therapeutic Interventions. Journal of Neurodegenerative Diseases. 2013 Dec 30;2013:1–8. doi:10.1155/2013/563481