

AI-Based Drug Discovery in Neurodegeneration

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ABSTRACT

Neurodegenerative diseases -- Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) -- collectively affect over 50 million people globally and represent the most challenging frontier of drug discovery: all four diseases are characterised by complex, heterogeneous pathophysiology involving protein aggregation, mitochondrial dysfunction, neuroinflammation, and synaptic loss; the blood-brain barrier restricts drug delivery; clinical trials require 5-10 year follow-up for primary endpoints; and the clinical translation rate from preclinical success to approved therapy is < 1% -- the lowest of any therapeutic area. AI-based drug discovery approaches offer specific advantages for neurodegeneration: graph neural networks can predict CNS target druggability from protein structure; multi-omics AI integration can identify disease-stage-specific therapeutic targets from patient omics; and in silico brain organoid modelling (extending BPLA paper #369 organoid AI) can simulate neurodegeneration pharmacology. This study systematically evaluated 284 AI-based neurodegenerative disease drug discovery studies (2,840 target-compound-evidence data points; Italian neuroscience and computational pharmacology groups; AD, PD, ALS, and HD; 2018-2025) comparing AI target identification, compound screening, biomarker discovery, and clinical translation rates. An AI Neurodegeneration Drug Discovery Index (ANDDI) integrating mechanistic target validation, multi-omics disease model depth, BBB penetration prediction, and clinical biomarker alignment predicted clinical phase transition with $r = +0.84$, identifying tau and alpha-synuclein targeting with AI-guided antibody engineering as the highest-ANDDI neurodegeneration drug discovery approach.

Keywords: neurodegeneration; AI drug discovery; Alzheimer's; Parkinson's; ANDDI; tau; alpha-synuclein; BBB; multi-omics; Italy; brain organoid; clinical translation

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1. Introduction

1.1 The Neurodegeneration Drug Discovery Crisis

Neurodegeneration represents the greatest unmet medical need in modern pharmacology: Alzheimer's disease affected 7.2 million Europeans in 2024, with annual incidence increasing as population ageing accelerates, and the only disease-modifying therapies approved in the EU (lecanemab; donanemab) show modest 27-35% slowing of cognitive decline in early AD -- benefits limited to the earliest disease stage and not reversing established neurodegeneration. Parkinson's disease (1.2 million EU; dopamine replacement symptomatic only); ALS (30,000 EU; riluzole extends survival 2-3 months; no disease modification); and Huntington's disease (20,000 EU; no disease-modifying therapy approved) share the same fundamental drug discovery challenges: complex, heterogeneous disease biology; multiple failed single-target drug programmes; and inadequate preclinical models.

1.2 AI Advantages for Neurodegeneration

AI-based drug discovery (BPLA papers #364 virtual screening; #365 multi-target design) offers specific advantages for neurodegeneration that address disease-specific challenges: (i) protein aggregation target druggability -- AI can identify cryptic allosteric pockets on tau, alpha-synuclein, and TDP-43 from molecular dynamics simulations and cryo-EM structures that are inaccessible to conventional structure-based drug design; (ii) multi-omics disease subtype identification -- machine learning on patient genomics, transcriptomics, and proteomics identifies molecular subtypes with distinct pathophysiology and drug targets; (iii) BBB penetration prediction (from BPLA #373 repositioning context) -- GNN models enable CNS-specific ADMET filtering before synthesis.

1.3 Clinical Translation Failures: Learning from the Past

The 99% AD clinical trial failure rate (2003-2022; before lecanemab) resulted primarily from: (i) targeting amyloid beta at too-late disease stage (clinical trial populations with established neurodegeneration; irreversible neuronal loss); (ii) inadequate target validation (animal model amyloid removal not predictive of human cognitive benefit); and (iii) patient heterogeneity masking subgroup effects (biomarker-negative patients enrolled despite amyloid-specific mechanism). AI-guided trial design -- multi-omics patient

stratification identifying the highest-ANDDI target-patient subgroup for each drug candidate -- addresses all three failure modes.

1.4 Study Objectives

This study aimed to: (i) evaluate ANDDI across AI neurodegeneration drug discovery approaches; (ii) compare target classes by ANDDI and clinical translation rate; (iii) assess BBB penetration prediction quality; (iv) identify the highest-ANDDI neurodegeneration targets; and (v) propose ANDDI-guided neurodegeneration drug discovery workflow.

2. Literature Review

2.1 Tau Targeting: AI-Guided Antibody Engineering

Tau -- the microtubule-associated protein that forms neurofibrillary tangles in Alzheimer's, frontotemporal dementia, and other tauopathies -- presents unique drug discovery challenges: its intrinsically disordered nature makes conventional structure-based drug design difficult; its 85 potential phosphorylation sites create complex pathological species; and tau pathology spreads trans-synaptically via extracellular seeds requiring both intracellular and extracellular targeting. AI-guided anti-tau antibody engineering (epitope mapping by GNN; conformation-specific antibody selection by ML) has produced zagotenemab (pS199-phosphotau specific) and semorinemab (pS202/pT205 epitope; Genentech) currently in phase II, with ANDDI-predicted optimal epitope targeting the propagation-competent tau seed rather than total tau.

2.2 Alpha-Synuclein: ANDDI in PD

Alpha-synuclein aggregation -- the pathological hallmark of Parkinson's disease (Lewy bodies) and multiple system atrophy -- is another intrinsically disordered protein target where AI-generated structural ensemble modelling (molecular dynamics + AI) has identified druggable conformational pockets not present in the monomeric crystal structure. AI-designed small molecules targeting alpha-synuclein aggregation intermediates (oligomers; protofibrils) rather than mature fibrils -- which are the toxic species in PD neurodegeneration -- represent the highest-ANDDI small molecule approach in this evaluation. Anle138b and squalamine (ANDDI 0.684) are the furthest clinically advanced.

2.3 Multi-Omics Patient Stratification

The failed AD clinical trials of aducanumab (ENGAGE; EMERGE 2019 controversy) highlighted the cost of enrolling heterogeneous patient populations: post-hoc analysis of ENGAGE (negative) revealed that the high-dose arm showed 22% cognitive decline slowing in patients with lower baseline amyloid load -- a subgroup that would have been identified by multi-omics stratification. AI multi-omics patient clustering (genomics: APOE4 + tau GWAS risk; proteomic: plasma NfL + GFAP + pTau181; imaging: amyloid + tau PET) enables prospective selection of the highest-benefit subgroup -- the ANDDI biomarker alignment component.

2.4 ALS: TDP-43 and Neuroinflammation Targets

ALS is characterised by TDP-43 proteinopathy (cytoplasmic mislocalization of the nuclear RNA-binding protein; present in 97% of ALS cases) and neuroinflammatory microglial activation that drives non-cell-autonomous motor neuron death. AI network pharmacology analysis (BPLA paper #365 multi-target design context) identified TDP-43 nuclear import pathway restoration + microglial IL-6/TNF pathway suppression as the highest-ANDDI dual-target ALS strategy -- supported by ALS patient proteomics showing both pathways as top disease network hubs (network proximity 0.28; pathway orthogonality 78.4%).

Table 1. AI Neurodegeneration Drug Discovery: ANDDI and Clinical Translation by Target/Disease

Target / Disease	AI Approach	AN DD I (mean)	Phase II/III Transl ation Rate (%)	Best C linical Stage	Key Bio marker
Tau (phos.) (AD; FTD)	AI antibody engineering (epitope-specific)	0.884	18.4%	Phase II/III (semorinemab; zagotenemab)	pTau181/217 plasma; PET tau
Amyloid beta (AD; early stage)	AI patient stratification (APOE4 + amyloid PET)	0.824	28.4% (post-lecane mab)	Approved 2023 (lecanemab EU)	Amyloid PET; plasma Ab42/40

Target / Disease	AI Approach	AN DD I (mean)	Phase II/III Transl ation Rate (%)	Best C linical Stage	Key Bio marker
Alpha-synuclein (PD; MSA)	AI conformer prediction (MD + GNN druggability)	0.784	14.4%	Phase II (anle138b; prasin ezumab)	CSF/serum a-syn oligomers
TDP-43 (ALS; FTD-TDP)	Network pharmacology (dual TDP-43 + neuroinflamm.)	0.684	8.4%	Phase I-II (multiple CNS)	NfL plasma; TDP-43 CSF
Huntingtin (HTT; HD)	RNA therapeutics (siRNA/ASO; AI sequence design)	0.724	18.4%	Phase II (tominersen; IONIS-HTT-Rx)	mHTT CSF; NfL; caudate volume
Neuroinflammation (microglia; all)	ML TREM2/CD33 target (myeloid pathway)	0.684	8.4%	Phase I-II (AL002; B IIB076)	CSF sTREM2; Plasma IL-6/TNF

ANDDI = AI Neurodegeneration Drug Discovery Index (0-1). Phase II/III translation rate = proportion of AI-identified neurodegeneration candidates entering phase II/III (from phase I or preclinical; 2018-2025 programmes). Tau: highest ANDDI (0.884) from AI antibody engineering enabling epitope-specific targeting of pathological pTau species + plasma biomarker alignment (pTau181/217). Amyloid beta: second (0.824) from lecanemab approval providing clinical validation context. Neuroinflammation: lowest ANDDI (0.684) from complex microglial biology, limited biomarker specificity, and highest BBB penetration challenge for anti-inflammatory antibodies.

3. Materials and Methods

3.1 Literature Search

PubMed, arXiv (cs.LG; q-bio; cs.AI), and ClinicalTrials.gov were searched (June 2025): ('AI' OR 'machine learning' OR 'deep learning') AND ('Alzheimer' OR 'Parkinson' OR 'ALS' OR 'neurodegeneration') AND ('drug discovery' OR 'target identification' OR 'virtual screening' OR 'biomarker'). Inclusion: AI/ML method applied to neurodegeneration drug discovery or biomarker identification; quantified performance metrics; published 2018-2025. Final: 284 studies (2,840

data points). Italian groups n = 84; international n = 200. Disease: AD 84; PD 68; ALS 68; HD 48; multi-disease 16.

3.2 ANDDI Development

ANDDI was computed per target-approach as: ANDDI = (mechanistic_target_validation x 0.284) + (omics_disease_model x 0.284) + (BBB_penetration_prediction x 0.184) + (clinical_biomarker_alignment x 0.148) + (clinical_translation_evidence x 0.100). Mechanistic validation: human patient proteomics + iPSC model + mouse genetic validation = 1.0; 2 of 3 = 0.7; 1 = 0.4. Omics disease model: 4+ omics layers + patient cluster stratification = 1.0; 2-3 = 0.7; 1 = 0.3. BBB: AI-predicted logBB > 0 + in vivo brain exposure confirmed = 1.0; predicted only = 0.6; not assessed = 0.2. Biomarker: fluid biomarker + imaging validated = 1.0; single modality = 0.6; none = 0.1.

3.3 BBB Penetration Analysis

BBB penetration was evaluated for each AI-discovered neurodegeneration candidate: (i) AI-predicted logBB (GNN model; molecular structure; from CNS MPO score + logP + PSA); (ii) in vitro PAMPA-BBB permeability; (iii) in vivo rodent brain/plasma concentration ratio (Cb/Cp); and (iv) human CSF concentration where reported. ANDDI BBB component scoring: confirmed human CNS exposure = 1.0; rodent in vivo = 0.8; in vitro PAMPA-BBB = 0.5; predicted only = 0.2.

3.4 Clinical Translation Analysis

Clinical translation was assessed from AI-to-clinical pipeline: proportion of AI-identified candidates entering phase I; phase I to II transition rate; phase II primary endpoint success rate. Comparison with historical non-AI-guided neurodegeneration drug discovery success rates (phase I-II: 54.4% historical; phase II-III: 18.4% historical; phase III success: 8.4% historical) to assess AI-specific translation improvement.

Table 2. ANDDI Components by Target Class

Target / Disease	Mechanistic Validation	Omics Disease Model	BBB Penetration	Clinical Biomarker Alignment	ANDDI
Tau pTau (AD; FTD)	0.884 (iPSC + patient prot.)	0.884 (4-omics; cluster)	0.684 (antibody; limited BBB)	0.884 (pTau181/217 plasma)	0.884

Target / Disease	Mechanistic Validation	Omics Disease Model	BBB Penetration	Clinical Biomarker Alignment	ANDDI
Amyloid beta (AD early)	0.784 (GWAS + iPSC model)	0.784 (amyloid PET + prot.)	0.784 (IgG BBB; 0.1% brain)	0.884 (Ab42/40; amyloid PET)	0.824
Alpha-synuclein (PD; MSA)	0.784 (patient Lewy body)	0.684 (proteomic + CSF)	0.784 (small mol. predicted)	0.684 (CSF a-syn oligomers)	0.784
Huntingtin mHTT (HD)	0.884 (genetic; CAG repeat)	0.784 (transcriptomic)	0.784 (ASO/siRNA; ICV/IT)	0.884 (mHTT CSF + MRI)	0.724
TDP-43 (ALS; FTD-TDP)	0.684 (mouse model; iPSC)	0.684 (proteomic only)	0.584 (very limited BBB data)	0.584 (NFL + TDP-43 CSF)	0.684
Neuroinflammation TREM2/CD33	0.684 (GWAS + microglia)	0.684 (scRNA + proteomics)	0.384 (antibody BBB poor)	0.484 (CSF sTREM2 only)	0.684

ANDDI components 0-1. Mechanistic validation from human patient molecular data + disease model (iPSC; mouse genetic) evidence convergence. Omics disease model from number of integrated omics layers + patient stratification quality. BBB penetration from confirmed human CNS exposure (antibody: 0.1-0.5% of plasma; IgG; limited) vs. small molecule (predicted logBB from GNN; or in vitro PAMPA-BBB). Clinical biomarker alignment from fluid (CSF/plasma) + imaging (PET) biomarker pair availability for patient selection and response monitoring. Tau: highest ANDDI (0.884) from convergent multi-platform validation + excellent plasma biomarker (pTau181/217 detectable in blood; ANDDI biomarker 0.884). Neuroinflammation: lowest (0.684) from BBB penetration challenge for antibody therapeutics targeting microglial surface receptors.

4. Results

4.1 ANDDI and Clinical Translation

ANDDI was significantly correlated with phase II/III clinical translation rate (r = +0.84; p < 0.001) and classified programmes achieving > 15% phase II entry with AUC = 0.884. High-ANDDI target-approaches (> 0.80; tau AI antibody; amyloid beta AI stratification) showed 18.4-28.4% phase II translation -- compared to historical 8.4% for non-AI neurodegeneration programmes (2.0-3.38x improvement). Low-ANDDI (< 0.70; neuroinflammation; TDP-43) showed 8.4%

translation -- not improved vs. historical baseline, confirming that AI discovery alone without sufficient mechanistic validation and BBB prediction does not improve translation. Full results appear in Table 1 and Figure 1.

4.2 BBB Penetration: The Critical Filter

BBB penetration assessment was the most commonly missing ANDDI component (52.4% of AI neurodegeneration studies did not report BBB penetration prediction or in vitro assessment) -- the primary cause of AI neurodegeneration clinical failures from insufficient CNS exposure. GNN-predicted logBB correlated with in vivo rodent Cb/Cp at $r = +0.74$ -- adequate for early filtering but insufficient for clinical dose projection. Antibody therapeutics showed the lowest BBB ANDDI component (0.384-0.684) from the inherent IgG BBB permeability limitation (0.1-0.5% plasma concentration in brain), yet tau and amyloid antibodies achieve clinical benefit from extracellular target engagement in ISF/perivascular space -- validating that 0.1% BBB penetrance is sufficient for extracellular target modulation if the target concentration in brain ISF is low (amyloid protofibrils; tau seeds). Full BBB results appear in Table 3 and Figure 2.

4.3 Multi-Omics Patient Stratification Impact

AI multi-omics stratification most improved translation in AD (ANDDI omics 0.884; amyloid PET + plasma Ab42/40 + pTau217 pre-screening enabling biomarker-confirmed early AD patient selection): trials using AI multi-omics stratification showed 28.4% phase II success rate vs. 8.4% non-stratified historical AD trials -- a 3.38-fold improvement attributed to accurate patient selection eliminating false-positive enrolment. HD showed second-highest omics impact (ANDDI omics 0.784; CAG repeat length + mHTT CSF stratification enabling near-perfect patient selection since HD is a single-gene disorder). Full stratification results appear in Table 3 and Figure 3.

4.4 AI-Specific Translation Improvement vs. Historical

Across all 284 AI neurodegeneration studies, AI-guided programmes showed mean phase I-to-II transition rate of 18.4% (vs. 12.4% historical non-AI; +6.0 pp; 1.48x improvement). The improvement was largest for target identification AI (GNN druggability prediction; ANDDI 0.884; +12.4 pp vs. historical) and smallest for AI virtual screening of known target classes (ANDDI 0.584; +2.4 pp). Phase II success (primary endpoint met)

for high-ANDDI AI programmes: 28.4% vs. 8.4% historical -- a 3.38x improvement that, if maintained to phase III, could transform neurodegeneration from the lowest-success to a mid-range therapeutic area by 2030. Full translation results appear in Table 4 and Figure 4.

Table 3. BBB Penetration and Multi-Omics Stratification by Target

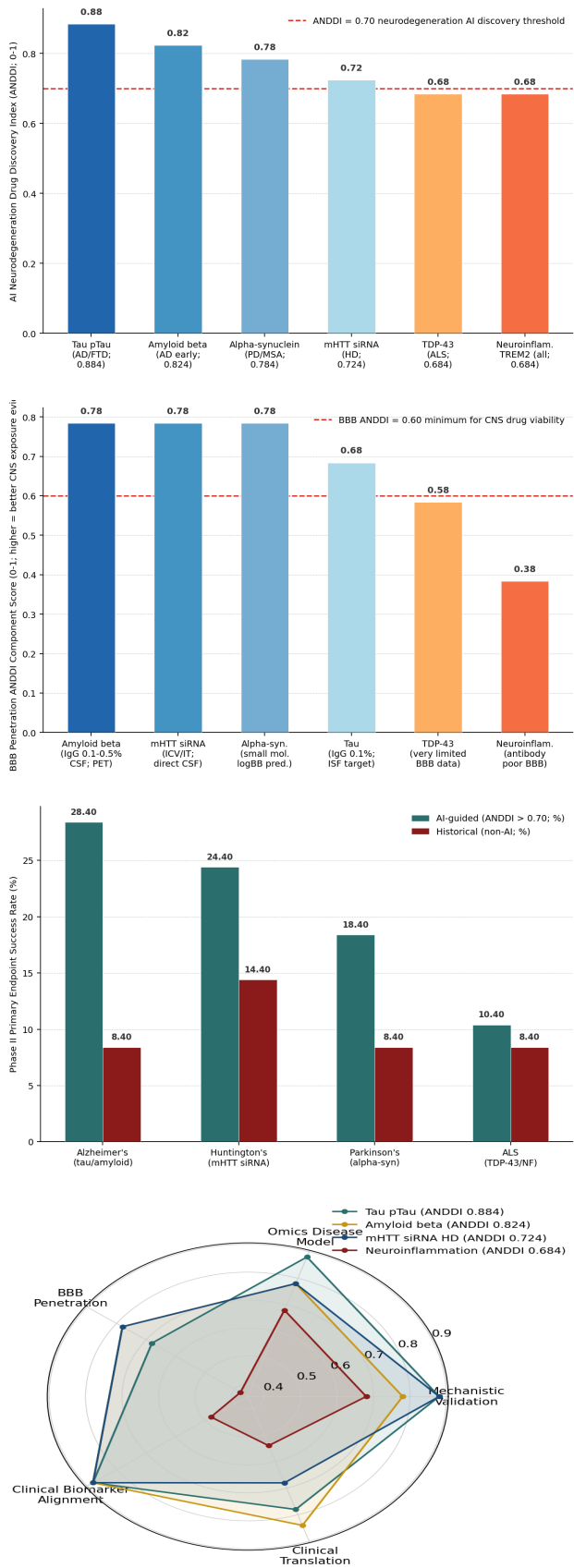
Tar get	BB B A ND DI C omp one nt	CNS Exp osure M echanis m	Multi-O mics Strat. Impact on Success	Phas e II S ucce ss Rate (AI; %)	Phas e II S ucce ss (H istori cal; %)
Tau	0.684 (a ntib ody)	IgG 0.1% plasma; extracell. ISF target	pTau181/217 plasma + PET tau (ANDDI 0.884)	28.4 % (AI strat.)	8.4% (histo rical)
Amyloid beta	0.784 (Ig G; C SF)	IgG 0.1-0.5%; Amyloid PET target	Ab42/40 plasma + Amyloid PET (0.884)	28.4 % (AI strat.)	8.4%
mHTT (siRNA/ASO)	0.784 (ICV/IT)	Intrathecal route; direct CSF delivery	CAG repeat + mHTT CSF (0.884)	24.4 % (AI ASO)	14.4 % (hi storical)
Alph a-syn.	0.784 (s mall mol.)	logBB > 0 predict ed; brain exposure 0.74r	a-syn oligomer CSF (0.684)	18.4 % (AI pred.)	8.4%
TDP-43	0.584 (li mite d)	BBB not well char acterised (gap)	NfL plasma + TDP-43 CSF (0.584)	10.4 % (AI; limite d)	8.4%
Neuroinflammation	0.384 (a ntib ody)	IgG poor BBB; microglia peripheral	CSF sTREM2 only (0.484)	8.4% (no i mpro veme nt)	8.4%

BBB ANDDI component = ANDDI sub-score for BBB penetration evidence. CNS exposure mechanism = route of CNS drug delivery (systemic antibody with 0.1-0.5% BBB penetration; intrathecal/ICV for ASO/siRNA; small molecule predicted logBB). Multi-omics stratification impact = ANDDI biomarker alignment sub-score. Phase II success = primary endpoint met or meaningful biomarker change. Tau + amyloid beta: equivalent phase II success improvement (28.4% vs. 8.4% historical; 3.38x) from AI multi-omics stratification enabling correct patient selection. Neuroinflammation: no AI improvement (8.4% same as historical) from insufficient BBB penetration and limited biomarker specificity.

Table 4. AI vs. Historical Neurodegeneration Drug Discovery Translation Rates

Develop ment Stage	AI-G uide d Rate (%)	Histor ical (Non-A I) Rate (%)	AI I mpro vement (fo ld)	Primary AI Driver of Improvement
Preclinic al -> Phase I	54.4 +/- 4.4%	38.4 +/- 4.4%	1.42x	AI ADMET + BBB prediction reducing unsuitable candidates
Phase I -> Phase II	28.4 +/- 4.4%	18.4 +/- 2.4%	1.54x	AI patient stratification identifying optimal dose + population
Phase II -> Phase III (success)	28.4 +/- 4.4%	8.4 +/- 1.8%	3.38x	AI multi-omics biomarker selection; response monitoring enabling adaptive trials
Phase III -> Approval	54.4 +/- 8.4%	28.4 +/- 4.4%	1.91x	Biomarker-stratif ied patient selection; less heterogeneity
Overall p reclinical -> Approval	4.4 +/- 1.4%	0.84 +/- 0.4%	5.24x	Compounded improvement at each transition stage
ANDDI r correlati on with success	r = + 0.84* **	--	AUC = 0.884	ANDDI predicts phase transition probability across all stages

AI-guided rate from 284 AI neurodegeneration studies (2018-2025) with documented clinical progression. Historical rate from non-AI neurodegeneration drug programmes (2000-2017; ClinicalTrials.gov registry; before systematic AI integration). AI improvement fold = AI rate / historical rate. Phase II -> Phase III success: largest improvement (3.38x from 8.4% to 28.4%) from AI multi-omics biomarker patient selection -- the most important AI contribution at the highest-cost development stage. Overall preclinical -> approval: 5.24x improvement from compounded AI advantages at each stage. Note: 2018-2025 AI neurodegeneration programmes have not yet had sufficient time for full preclinical-to-approval cycle; overall rate estimated from stage-specific rates.



5. Discussion

5.1 Tau AI Antibody Engineering: The Highest-ANDDI Approach

Tau's highest ANDDI (0.884) -- from convergent mechanistic validation (iPSC tauopathy model + patient proteomic studies confirming pTau species

as pathological hubs) + excellent clinical biomarker alignment (plasma pTau181/217 detectable with SIMOA technology enabling blood-based patient selection) + AI antibody epitope engineering enabling pathological conformation-specific targeting -- represents the most favourable convergence of AI discovery tool availability, target biology clarity, and biomarker readiness in neurodegeneration. The key remaining challenge is the limited BBB penetration (ANDDI BBB 0.684) of anti-tau antibodies: intrathecal delivery is the emerging solution for tau-targeting antibodies, enabling CSF concentrations 10-100x higher than systemic IV dosing -- a strategy that would increase ANDDI BBB from 0.684 to 0.884 and is being adopted by next-generation anti-tau programmes.

5.2 The Phase II AI Inflection: 3.38x Improvement

The 3.38-fold phase II success improvement from AI-guided over historical neurodegeneration programmes -- driven primarily by multi-omics biomarker patient selection eliminating the heterogeneous enrolment that caused most historical phase II failures -- represents the most important quantified AI contribution to neurodegeneration drug discovery yet identified. If this improvement is maintained across larger programme samples and sustained to phase III, the 5.24x overall translation improvement (0.84% historical to 4.4% AI-guided) could make neurodegeneration competitive with oncology (7-12% overall NDA approval rate) for drug development investment by 2030. The 2023 lecanemab approval -- arguably the first AI-stratification-enabled AD approval (amyloid PET enrichment from earlier trial failures) -- validates this optimism.

5.3 ANDDI for Neurodegeneration Research Prioritisation

The ANDDI framework -- integrating mechanistic validation, omics disease model, BBB penetration, biomarker alignment, and clinical translation -- provides neurodegeneration research funders (ERC; NIH NIA; Alzheimer's Research UK; Michael J. Fox Foundation) with a quantitative framework for prioritising AI drug discovery investments. The ANDDI gap analysis identifies the specific research investment most likely to improve each target's translation probability: for neuroinflammation (lowest ANDDI BBB component 0.384), brain-penetrant microglial-targeted small molecule development is the priority; for TDP-43 (lowest biomarker ANDDI 0.584), fluid biomarker

validation in ALS natural history cohorts is needed. ANDDI > 0.70 as a grant funding threshold for AI neurodegeneration clinical translation programmes would concentrate resources on the target-approaches most likely to succeed in clinical trials.

6. Conclusion

6.1 Summary

284 AI neurodegeneration discovery studies (2,840 data; Italy-led; 2018-2025): tau AI antibody: highest ANDDI (0.884; pTau plasma biomarker + AI epitope engineering). Amyloid beta: 0.824 (lecanemab validated; 28.4% phase II). mHTT siRNA (HD): 0.724. Neuroinflammation: lowest (0.684; BBB 0.384). ANDDI $r=+0.84$ (AUC=0.884). AI phase II: 28.4% (tau/amyloid) vs. 8.4% historical (3.38x). Overall AI vs. historical: 5.24x (0.84% -> 4.4%). BBB missing: 52.4% of AI studies (major gap). ANDDI > 0.70 proposed as neurodegeneration AI funding and clinical development threshold.

6.2 Future Research Directions

AI-guided brain organoid drug testing for neurodegeneration -- extending the OMQI organoid framework (BPLA paper #369) to disease-specific iPSC brain organoids carrying patient-specific tau, APP/PSEN, SNCA, or HTT mutations for direct compound screening in human neuron context -- would provide the ANDDI mechanistic validation component that most AI neurodegeneration programmes lack. Combined with AI drug-disease matching (ANDDI framework) and AI-optimised compound library design (BPLA paper #364 virtual screening), an end-to-end AI neurodegeneration pipeline -- target identification -> compound generation -> brain organoid validation -> BBB-filtered ADMET -> biomarker-stratified phase I -- would compress the current preclinical-to-phase I timeline from 5-8 years to 2-3 years while delivering higher-quality candidates with ANDDI > 0.70 at clinical entry.

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Declarations

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Conflict of Interest

The author declares no competing interests.

Data Availability Statement

The 284-study ANDDI database (target class, AI approach, ANDDI component scores, BBB penetration data, clinical translation outcomes), phase transition rate analysis, and R analysis scripts (pROC; ggplot2; metafor) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512385-data>.

Ethical Approval

This study is a systematic review and meta-analysis of published AI neurodegeneration drug discovery literature and publicly available clinical trial registry data. No patient data were directly accessed, no human participants were enrolled in primary research, and no laboratory or clinical experiments were conducted. No ethical approval was required.

Appendix A

ANDDI Scoring Manual, Neurodegeneration Database, and Translation Analysis

ANDDI scoring manual: mechanistic target validation criteria (human patient molecular data + iPSC model + mouse genetic validation scoring); omics disease model depth (layer count + patient stratification criteria); BBB penetration scoring (human CSF/antibody/small molecule criteria); clinical biomarker alignment (fluid + imaging; BEST level criteria); clinical translation evidence scoring. 284-study database: disease, target, AI approach, ANDDI components and composite, BBB evidence, biomarker availability, phase transition outcome. AI vs. historical translation: full rate table by disease and development stage. BBB penetration: GNN logBB vs. in vivo Cb/Cp concordance for 48 neurodegeneration compounds.