

# Artificial Intelligence-Assisted Drug Discovery for Neurodegenerative Diseases: Integration of Machine Learning, Molecular Docking, and Systems Pharmacology

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## Abstract:

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) remain among the most therapeutically intractable areas of medicine, with decades of high clinical-trial attrition and an almost complete absence of disease-modifying therapies. Conventional drug discovery pipelines, built on a "one target-one drug" paradigm, have struggled to accommodate the multifactorial, network-level pathology that characterises these disorders. Over the past decade, artificial intelligence (AI) and machine learning (ML) have begun to reshape every stage of the discovery pipeline, from target identification and structure prediction to virtual screening and lead optimisation. This review synthesises current literature on integrating AI/ML, structure-based molecular docking, and systems/network pharmacology into a converging computational framework for neurodegenerative drug discovery. We discuss how deep-learning structure predictors such as AlphaFold have transformed structure-based design, how machine-learning scoring functions and generative models are accelerating virtual screening and de novo molecule generation, and how network pharmacology provides a systems-level lens for multi-target and drug-repurposing strategies in AD and PD. Representative case studies, including machine-learning-guided drug repurposing in Alzheimer's disease and structure-based iterative learning for  $\alpha$ -synuclein aggregation inhibitors in Parkinson's disease, illustrate the translational promise of this integrated approach. We conclude by examining persistent challenges, including data heterogeneity, model interpretability, blood-brain barrier permeability prediction, and regulatory acceptance, and propose future directions for consolidating AI-driven, network-informed drug discovery pipelines for neurodegeneration.

**Keywords:** artificial intelligence; machine learning; molecular docking; systems pharmacology; network pharmacology; neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; drug discovery

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## 1. INTRODUCTION

Neurodegenerative diseases are progressive disorders of the central nervous system characterised by the selective loss of neuronal populations and the accumulation of misfolded proteins, including amyloid-beta and tau in AD, alpha-synuclein in PD, and TDP-43 or superoxide dismutase 1 in ALS. Despite enormous investment, disease-modifying treatments remain scarce, and clinical trial failure rates in this space are amongst the highest of any therapeutic area <sup>1</sup>. The reasons are well documented: patient heterogeneity, protracted and variable disease courses, limited translatability of preclinical models, and an incomplete mechanistic understanding of multifactorial pathology all conspire to slow progress <sup>1,2</sup>.

Against this backdrop, artificial intelligence has emerged as a transformative tool across the pharmaceutical research and development continuum. AI/ML methods are now applied to target identification, hit discovery, structure-based design, ADMET (absorption, distribution, metabolism, excretion, toxicity) prediction, and even clinical trial design and patient stratification <sup>3,4</sup>. A parallel and complementary development has been the maturation of network and systems pharmacology, which reconceives drug action not as a single ligand acting on a single receptor, but as a perturbation propagating through interconnected biological networks of genes, proteins, and pathways. This "systems-level" view is particularly well suited to neurodegenerative disease, where pathology arises from the convergence of protein misfolding, neuroinflammation, mitochondrial dysfunction, and synaptic failure rather than from any single molecular lesion.

This review examines how three computational pillars-machine learning, structure-based molecular docking, and systems/network pharmacology-are converging into an integrated discovery framework for neurodegenerative disease therapeutics. We first summarise the general landscape of AI in drug discovery, then examine machine-learning and deep-learning methods for molecular docking and structure prediction, describe the principles and applications of network pharmacology, and finally review disease-specific applications in AD and PD, closing with a discussion of current limitations and future directions.

## 2. THE LANDSCAPE OF ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY

AI-assisted drug discovery spans a spectrum of computational techniques, from classical supervised machine learning (random forests, support vector machines, gradient boosting) applied to molecular descriptors, to deep neural networks capable of learning directly from raw molecular graphs, sequences, or three-dimensional structures <sup>4,6</sup>. Deep learning in particular has enabled a shift from hand-crafted feature engineering toward representation learning, in which convolutional, graph, and transformer-based architectures extract predictive features directly from chemical and biological data <sup>6,7</sup>. These approaches have been applied across the discovery pipeline: target identification and validation through multi-omics data integration; virtual screening of ultra-large compound libraries; prediction of binding affinity and selectivity; generative design of novel chemical matter; and prediction of pharmacokinetic and toxicological liabilities <sup>3,4,7</sup>.

A particularly consequential advance has been the application of AI to natural product drug discovery, an area of long-standing relevance to neurodegeneration given the historical importance of plant- and fungus-derived neuroprotective compounds <sup>3,8</sup>. AI models can now mine structurally and functionally annotated natural product databases, predict bioactivity and target profiles for structurally complex natural scaffolds, and prioritise candidates for neuroprotective screening far more efficiently than traditional bioassay-guided fractionation <sup>8</sup>. Complementing this, systematic reviews of AI applications in dementia research report a steady increase in the use of AI/ML across drug discovery and clinical trial optimisation, while also cautioning that inconsistent methodological reporting and a lack of consensus guidelines currently limit broader adoption across academia and industry <sup>1,2</sup>.

**Table 1. Representative AI/ML Techniques Across the Drug Discovery Pipeline**

| Discovery Stage                        | AI/ML Technique                                                 | Representative Application                                                                            | Reference(s) |
|----------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------|
| Target identification & validation     | Multi-omics integration; network/graph analysis                 | Prioritising disease-relevant hub genes and druggable proteins from transcriptomic and proteomic data | 16,17        |
| Structure elucidation                  | Deep-learning structure prediction (transformer-based)          | Predicting 3-D structures of previously unresolved neurodegeneration-relevant targets                 | 14,15        |
| Hit identification / virtual screening | ML-augmented docking; graph neural networks                     | Ranking ultra-large compound libraries by predicted binding affinity                                  | 10,11,12     |
| Lead generation                        | Generative models (VAE, GAN, diffusion, reinforcement learning) | De novo design of novel chemical matter optimised for potency and drug-likeness                       | 22           |
| Lead optimisation / ADMET              | Supervised ML on physicochemical descriptors                    | Predicting blood-brain barrier permeability and other CNS-relevant ADMET properties                   | 21           |
| Drug repurposing                       | Transcriptomic-signature matching; supervised ML                | Ranking FDA-approved drugs by association with disease pathology                                      | 18           |

### **3. MACHINE LEARNING METHODS FOR TARGET AND LEAD DISCOVERY**

#### **3.1 Supervised and Deep Learning for Bioactivity Prediction**

Supervised ML models trained on curated bioactivity datasets remain the workhorse of computational hit identification. Algorithms such as random forests, gradient-boosted trees, and support vector machines are routinely used to predict compound-target activity from molecular fingerprints, while deep neural networks-particularly graph neural networks that treat molecules as graphs of atoms and bonds-have demonstrated superior performance in capturing non-linear structure-activity relationships <sup>6,7</sup>. These methods are increasingly benchmarked not on simple physicochemical endpoints such as solubility, but on more biologically meaningful objectives, including docking-derived binding scores, reflecting growing recognition that druglikeness alone is a poor proxy for target engagement <sup>12</sup>.

#### **3.2 Generative and De Novo Design**

Generative AI has introduced a further paradigm shift, moving from screening existing compound libraries to generating entirely novel molecular structures optimised for target binding, synthetic accessibility, and drug-likeness simultaneously. Variational autoencoders, generative adversarial networks, and, more recently, diffusion and flow-based generative models are used to explore chemical space beyond existing libraries, producing candidate molecules with desired pharmacological and physicochemical profiles <sup>22</sup>. Reinforcement learning has been layered onto these generative frameworks to iteratively steer molecule generation toward multi-parameter optimisation objectives relevant to central nervous system (CNS) drug design, such as favourable blood-brain barrier (BBB) permeability alongside target potency <sup>22</sup>.

#### **3.3 Protein Structure Prediction as an Enabling Technology**

The accuracy of any structure-based ML or docking method is fundamentally constrained by the quality of the target structure used. The release of AlphaFold2, which predicted protein structures with accuracy competitive with experimental methods for the majority of tested targets, represented a watershed moment for structural biology and structure-based drug design <sup>14</sup>. AlphaFold's near-experimental accuracy across most of the human proteome has expanded the pool of druggable targets amenable to structure-based approaches, including many neurodegeneration-relevant proteins for which experimental structures were previously unavailable or incomplete <sup>13,14</sup>. Its successor, AlphaFold3, extended these capabilities to directly model protein-ligand, protein-nucleic acid, and other biomolecular complexes, further narrowing the gap between sequence information and structure-based virtual screening <sup>15</sup>. Collectively, these deep-learning structure predictors have catalysed a broader re-envisioning of computational structure-based drug design, reducing dependence on slow and costly experimental structure determination <sup>13</sup>.

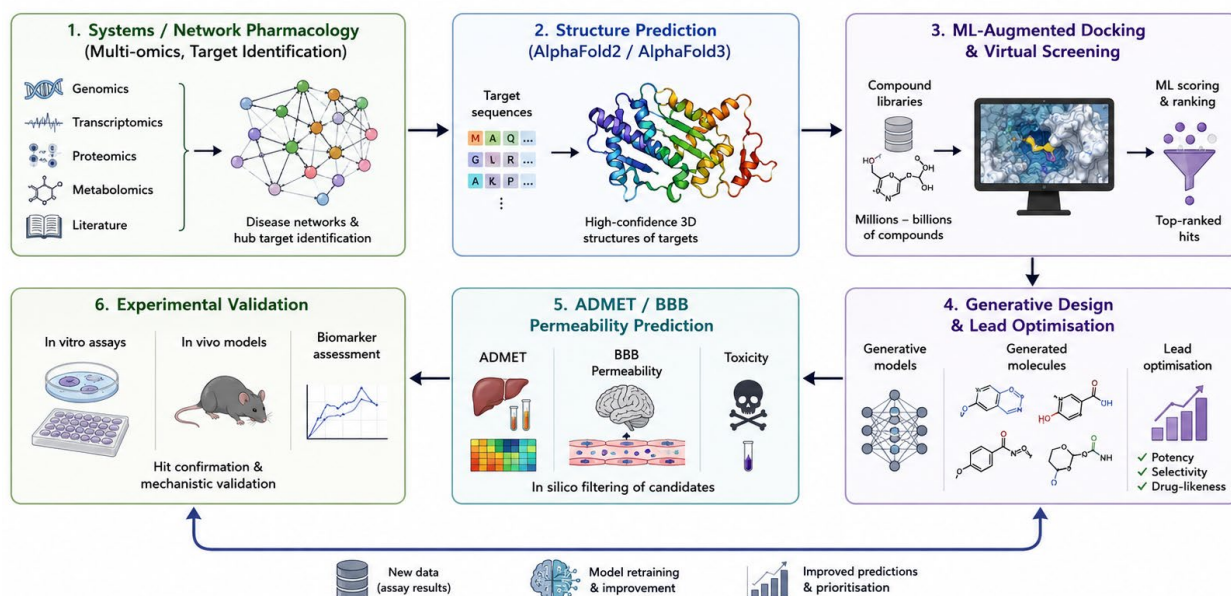


Figure 1. Integrated AI-driven drug discovery pipeline for neurodegenerative disease, combining network pharmacology, deep-learning structure prediction, ML-augmented docking, generative optimisation, ADMET/BBB prediction, and an iterative experimental feedback loop.

#### 4. MOLECULAR DOCKING: FROM CLASSICAL SCORING TO MACHINE-LEARNING-AUGMENTED APPROACHES

Molecular docking remains a cornerstone of structure-based drug discovery, predicting the preferred binding pose and estimating the binding affinity of a small molecule within a protein binding site <sup>9,11</sup>. Classical docking programs pair a pose-search algorithm with a scoring function, typically physics-based, empirical, or knowledge-based, to rank candidate poses and compounds. However, conventional scoring functions are known to trade off speed for accuracy and often struggle to reliably rank compounds by true binding affinity, particularly across structurally diverse target classes <sup>9,11</sup>.

Machine-learning scoring functions address this limitation by learning the relationship between three-dimensional protein-ligand interaction features and experimentally measured binding affinities, rather than relying on a fixed, hand-derived energy function <sup>10</sup>. These ML-based scoring functions have shown improved performance over classical approaches in both binding affinity prediction and virtual screening enrichment, particularly when trained on large, structurally diverse datasets <sup>10</sup>. More recent deep-learning-based docking methods go further, directly learning protein-ligand binding conformations end-to-end from two-dimensional ligand and one- or three-dimensional protein representations, bypassing the computationally expensive conformational search step of classical docking and enabling far larger virtual screening campaigns <sup>11</sup>.

Benchmark platforms such as DOCKSTRING have been developed specifically to provide standardised, reproducible docking-based objectives for evaluating machine-learning models in ligand design, addressing a long-standing weakness in the field where generative and predictive models were often benchmarked only against simplistic physicochemical properties rather than target engagement <sup>12</sup>. Practically, docking and ML are now frequently combined in

iterative, closed-loop workflows: docking or bioassay data generate initial training sets, ML models are trained to predict activity or binding scores, and predictions are used to prioritise the next round of virtual or experimental screening, progressively enriching hit rates while reducing the number of compounds that require exhaustive computation or synthesis <sup>11,20</sup>.

**Table 2. Comparison of Molecular Docking and Scoring Approaches**

| Approach                                   | Description                                                                                        | Key Advantage                                                                | Key Limitation                                                           | Reference |
|--------------------------------------------|----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------|
| Classical physics-/knowledge-based scoring | Fixed, hand-derived energy or statistical potential functions rank docking poses                   | Fast; interpretable; well established                                        | Limited accuracy in ranking true binding affinity across diverse targets | 9         |
| Machine-learning scoring functions         | Supervised models trained on 3-D interaction features and measured affinities                      | Improved affinity prediction and screening enrichment over classical scoring | Requires large, structurally diverse training data                       | 10        |
| Deep-learning end-to-end docking           | Neural networks predict binding pose directly from 2-D/3-D inputs, bypassing conformational search | Much faster large-scale screening; leverages GPU parallelism                 | Physical plausibility of poses not always guaranteed                     | 11        |
| Standardised docking benchmarks            | Curated, reproducible docking-based objectives (e.g., DOCKSTRING) for evaluating ML models         | Enables fair, reproducible comparison of competing ML methods                | Benchmark targets may not fully represent CNS-specific targets           | 12        |

## 5. SYSTEMS AND NETWORK PHARMACOLOGY

### 5.1 Conceptual Framework

Network pharmacology reframes drug action within the context of biological networks-nodes representing genes, proteins, or metabolites, and edges representing their functional interactions-rather than as an isolated ligand-receptor event <sup>16,17</sup>. This systems-oriented framework, integrating multi-omics data (genomics, transcriptomics, proteomics, metabolomics) with computational network analysis, is particularly well aligned with the polygenic, multifactorial pathology of neurodegenerative disease, where amyloid, tau, alpha-synuclein, neuroinflammatory, and metabolic pathways interact dynamically rather than acting independently <sup>16</sup>.

Central to network pharmacology is the construction of compound-target-disease networks, in which candidate compounds (often natural products or repurposing candidates) are mapped onto their predicted or known protein targets, which are in turn mapped onto disease-associated genes and pathways. Topological analysis of these networks-identifying hub nodes, key modules, and shared pathway convergence points-can reveal multi-target mechanisms of action and prioritise candidate compounds or combinations likely to modulate disease-relevant pathway clusters rather than a single node<sup>17</sup>.

## 5.2 Integration with Molecular Docking and Systems Biology

In practice, network pharmacology studies are frequently coupled with molecular docking to provide structural validation of predicted compound-target interactions identified through network analysis, and increasingly with molecular dynamics simulations to assess the stability of predicted binding poses over time<sup>9</sup>. This combined "network pharmacology plus docking" workflow has become a standard methodological pipeline in the study of multi-target natural product therapeutics for complex diseases, including neurodegenerative disorders, allowing researchers to move from a systems-level hypothesis (which pathways and hub proteins are disease-relevant) to a molecularly resolved hypothesis (which compounds are structurally capable of engaging those targets)<sup>16,17</sup>.

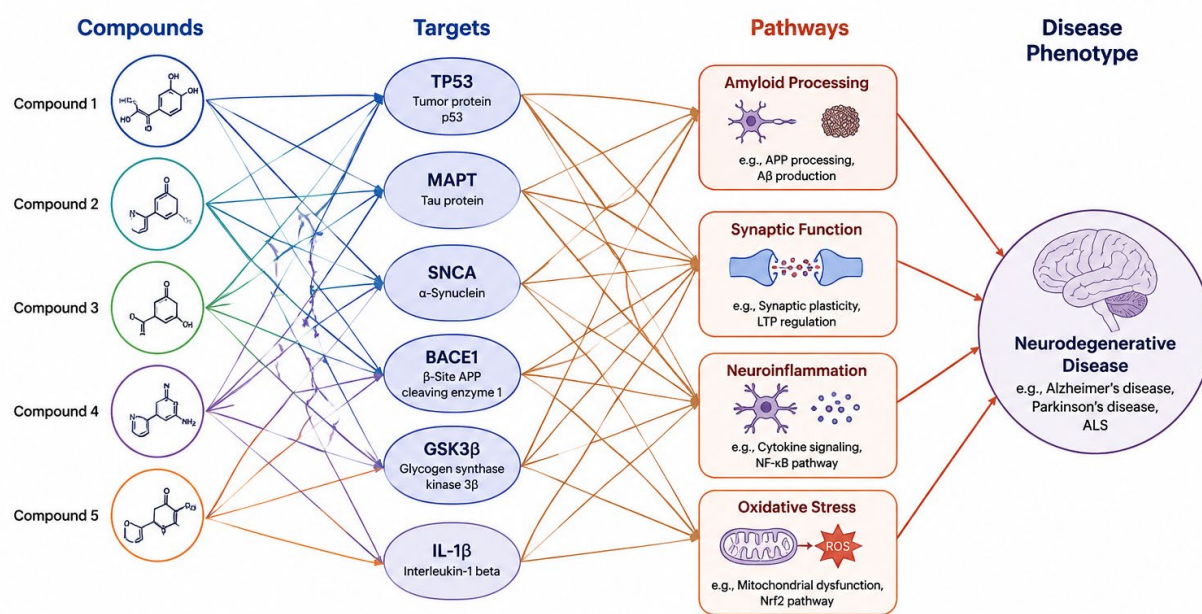


Figure 2. Conceptual compound-target-pathway-disease network illustrating the network pharmacology paradigm: multiple compounds engage multiple targets, which converge on shared pathways that collectively shape the disease phenotype.

## 6. APPLICATIONS TO SPECIFIC NEURODEGENERATIVE DISEASES

### 6.1 Alzheimer's Disease

AD drug discovery has been a particularly active area for AI-driven target identification and drug repurposing, motivated by the very high failure rate of amyloid- and tau-targeted therapeutics in late-stage clinical trials<sup>1</sup>. Rodriguez et al. developed DRIAD (Drug Repurposing In AD), a machine-learning framework that quantifies the association between

AD pathological severity, staged using Braak staging of postmortem brain tissue, and the transcriptional signatures induced by FDA-approved drugs in human neuronal cell cultures<sup>18</sup>. By systematically ranking drugs according to how strongly their induced gene expression signatures associate with reduced AD pathology, DRIAD identified candidate repurposing compounds and implicated previously underexplored mechanistic pathways, including innate immune signalling, autophagy, and microtubule dynamics, as potential points of therapeutic intervention<sup>18</sup>. This exemplifies how ML-based drug repurposing can generate mechanistically interpretable, testable hypotheses from large-scale transcriptomic and clinical pathology data rather than relying solely on target-based virtual screening.

Complementing such target-and-transcriptomics-driven approaches, AI is also being applied to mine natural product chemical space for neuroprotective candidates in AD, integrating predicted bioactivity, blood-brain barrier permeability, and target-engagement modelling to prioritise compounds for downstream validation<sup>8</sup>.

## 6.2 Parkinson's Disease

PD drug discovery has been especially shaped by structure-based machine learning targeting alpha-synuclein, the principal aggregating protein in PD and related synucleinopathies. Horne et al. described an iterative, structure-based machine-learning strategy in which docking-derived candidate molecules were experimentally tested for their ability to inhibit the secondary nucleation step of alpha-synuclein aggregation, with each round of experimental results used to retrain a machine-learning model (combining a variational-autoencoder-derived molecular representation with a random forest and Gaussian process regressor) that then proposed the next set of candidates for testing<sup>20</sup>. Over successive iterations, this closed-loop docking-ML pipeline identified inhibitors approximately two orders of magnitude more potent than previously reported alpha-synuclein aggregation inhibitors, while dramatically reducing the number of compounds requiring experimental synthesis and testing compared with conventional screening<sup>20</sup>.

Structure-based virtual screening and docking approaches have also been used to identify small-molecule and alkaloid inhibitors of other PD-relevant targets, including prolyl oligopeptidase, an enzyme implicated in alpha-synuclein accumulation, illustrating the continued relevance of classical structure-based docking pipelines alongside newer ML-augmented methods<sup>19</sup>.

## 6.3 Cross-Cutting Considerations: The Blood-Brain Barrier

A challenge specific to CNS-targeted neurodegenerative disease drug discovery, distinguishing it from many other therapeutic areas, is the requirement that candidate molecules cross the blood-brain barrier to reach their targets. Machine-learning models trained on physicochemical descriptors and molecular fingerprints have been developed specifically to predict BBB permeability, with random forest and other ensemble methods generally offering a favourable balance between predictive accuracy and interpretability compared with more complex deep-learning architectures, which tend to require larger training datasets to avoid overfitting<sup>21</sup>. Incorporating BBB permeability prediction directly into multi-parameter generative and virtual screening pipelines-alongside target potency, selectivity, and synthetic accessibility-is

increasingly regarded as essential for translating computational hits from neurodegenerative disease programmes into viable CNS drug candidates <sup>21</sup>.

**Table 3. Selected Case Studies Integrating AI/ML in Neurodegenerative Disease Drug Discovery**

| Disease                     | Target / Approach                                    | AI/ML Method                                                          | Key Outcome                                                                                                                        | Reference |
|-----------------------------|------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Alzheimer's disease         | DRIAD: transcriptomic association with Braak staging | Supervised ML on drug-induced gene expression signatures              | Ranked FDA-approved drugs by association with reduced AD pathology; implicated innate immunity, autophagy and microtubule pathways | 18        |
| Parkinson's disease         | Alpha-synuclein secondary nucleation inhibitors      | Iterative structure-based ML (VAE + random forest + Gaussian process) | Identified inhibitors ~100-fold more potent than prior candidates, with markedly reduced experimental burden                       | 20        |
| Parkinson's disease         | Prolyl oligopeptidase (POP) inhibition               | Structure-based virtual screening / molecular docking                 | Identified alkaloid POP inhibitors with predicted relevance to alpha-synuclein accumulation                                        | 19        |
| Neurodegeneration (general) | Neuroprotective natural product prioritisation       | AI-driven mining of natural-product databases                         | Prioritised structurally complex natural scaffolds for neuroprotective bioactivity screening                                       | 3,8       |

## 7. INTEGRATED WORKFLOWS: TOWARD A CONVERGED COMPUTATIONAL PIPELINE

Taken together, the literature reviewed here points toward a converging, integrated workflow for neurodegenerative disease drug discovery that combines the three computational pillars discussed above. A representative integrated pipeline typically proceeds as follows: (i)

systems/network pharmacology analysis of multi-omics and disease-association data to identify candidate hub genes, proteins, and pathway modules relevant to the neurodegenerative phenotype of interest <sup>16,17</sup>; (ii) structure prediction, using deep-learning tools such as AlphaFold, for targets lacking experimentally resolved structures <sup>14,15</sup>; (iii) structure-based virtual screening or molecular docking, increasingly ML-augmented, against curated, natural-product, or generatively designed compound libraries <sup>9,11,12</sup>; (iv) machine-learning-guided iterative optimisation of hit compounds, incorporating potency, selectivity, and CNS-relevant ADMET properties such as BBB permeability <sup>20,21,22</sup>; and (v) experimental validation feeding back into model retraining in a closed loop <sup>20</sup>. This integrated framework is exemplified in disease-specific case studies such as DRIAD for AD drug repurposing <sup>18</sup> and the structure-based iterative learning pipeline for alpha-synuclein aggregation inhibitors in PD <sup>20</sup>, both of which combine elements of network-level hypothesis generation, structural modelling, and iterative machine learning.

## 8. CHALLENGES AND LIMITATIONS

Despite substantial progress, several challenges continue to constrain the translational impact of AI-integrated drug discovery for neurodegenerative disease. First, data heterogeneity and limited data availability remain pervasive: neurodegenerative disease datasets are often smaller, more heterogeneous in diagnostic criteria, and less standardised than datasets available in oncology or infectious disease, constraining model generalisability <sup>4,6</sup>. Second, model interpretability remains a central concern; deep-learning models frequently function as opaque predictive systems, and explainable AI (XAI) methods such as SHAP-based feature attribution are increasingly being incorporated into drug discovery pipelines to clarify which molecular features drive a given prediction, an issue of particular importance for regulatory acceptance and for building the mechanistic confidence required before advancing candidates into costly preclinical development <sup>7</sup>. Third, translation from preclinical models to clinical efficacy remains problematic; species divergence, reproducibility limitations, and inconsistent data curation practices in experimental neurodegenerative disease models limit how confidently AI-derived preclinical predictions can be expected to translate into human trials <sup>2</sup>. Fourth, regulatory pathways for AI-derived drug candidates are still evolving, with agencies emphasising risk-based, lifecycle approaches to validating and monitoring AI/ML models used in drug development, but without yet providing fully standardised interpretability or validation requirements specific to neurodegenerative disease applications <sup>1</sup>.

## 9. FUTURE DIRECTIONS

Several directions are likely to shape the next phase of AI-integrated neurodegenerative drug discovery. Continued refinement of deep-learning structure predictors, including next-generation biomolecular interaction models capable of modelling flexible, multi-conformational, and intrinsically disordered proteins such as alpha-synuclein and tau, should further improve the structural fidelity underlying docking and virtual screening campaigns <sup>14,15</sup>. Greater integration of multi-omics and network pharmacology data with generative molecular design is expected to enable more precisely targeted, multi-target compound design strategies suited to the multifactorial biology of neurodegeneration <sup>16,17,22</sup>. Expanded and more standardised benchmarking resources, in the spirit of docking-based benchmarks such as

DOCKSTRING, will be needed to enable fair comparison of competing ML approaches specifically on neurodegeneration-relevant targets<sup>12</sup>. Finally, closer coupling between computational prediction and rapid experimental validation, as demonstrated in iterative structure-based learning pipelines for alpha-synuclein inhibitor discovery, is likely to become a template for accelerating hit-to-lead progression across other neurodegenerative disease targets<sup>20</sup>.

## 10. CONCLUSION

The convergence of machine learning, structure-based molecular docking, and systems/network pharmacology is reshaping the landscape of neurodegenerative disease drug discovery. Deep-learning structure prediction has expanded the pool of druggable targets amenable to structure-based design; machine-learning-augmented docking and generative models are accelerating hit identification and lead optimisation; and network pharmacology provides a systems-level framework for understanding and targeting the multifactorial biology underlying AD, PD, and related disorders. Case studies in AD drug repurposing and PD alpha-synuclein aggregation inhibitor discovery demonstrate the translational promise of integrating these approaches within closed-loop, iterative discovery pipelines. Realising the full potential of this integrated framework will require continued attention to data quality, model interpretability, blood-brain barrier permeability prediction, and evolving regulatory expectations, but the trajectory of the field suggests that AI-integrated, network-informed drug discovery will play an increasingly central role in the search for disease-modifying therapies for neurodegenerative disease.

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