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REVIEW

New insights into translational research in Alzheimer's disease guided by artificial intelligence, computational and systems biology

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Abstract Alzheimer's disease (AD) is characterized by cognitive and functional deterioration, with pathological features such as amyloid-beta (Aβ) aggregates in the extracellular spaces of parenchymal neurons and intracellular neurofibrillary tangles formed by the hyperphosphorylation of tau protein. Despite a thorough investigation, current treatments targeting the reduction of Aβ production, promotion of its clearance, and inhibition of tau protein phosphorylation and aggregation have not met clinical expectations, posing a substantial obstacle in the development of drugs for AD. Recently, artificial intelligence (AI), computational biology (CB), and systems biology (SB) have emerged as promising methodologies in AD research. Their capacity to analyze extensive and varied datasets facilitates the identification of intricate patterns, thereby enriching our comprehension of AD pathology. This paper provides a comprehensive examination of the utilization of AI, CB, and SB in the diagnosis of AD, including the use of imaging omics for early detection, drug discovery methods such as lecanemab, and complementary therapies like phototherapy. This review offers novel perspectives and potential avenues for further research in the realm of translational AD studies.

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1. Introduction

1.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease that is prevalent worldwide. It has an insidious onset and progressive aggravation of symptoms, including cognitive decline and other neuropsychiatric symptoms. It is estimated that as of 2023, there will be a total of 416 million patients with dementia, prodromal AD, and preclinical AD worldwide, accounting for 22% of people aged 50 and over [1]. With the progression of genome sequencing and bioinformatics, the genes *APP*, *PSEN1*, *PSEN2*, *APOE4*, *SORL1*, *ABCA7*, and *TREM2* have been identified as being associated with the onset of AD. Additionally, factors such as low educational attainment, hypertension, hearing impairment, smoking, obesity during middle age, depression, physical inactivity, diabetes, social isolation, excessive alcohol consumption, head injuries, and exposure to air pollution have been recognized as risk factors for dementia[2-4]. As AD is one of the most lethal and burdensome diseases, it is necessary to elucidate the underlying mechanisms and develop corresponding intervention strategies. Existing hypotheses include: amyloid cascade, tau hyperphosphorylation, synaptic dysfunction and neurotransmitter imbalance, neuroinflammation, infectious disease hypothesis, intestinal microbial disruption, genetic mutation, oxidative stress, autophagy, formaldehyde accumulation, cholinergic and vascular hypotheses, etc., they all play a certain role in the development of AD[5,6]. The most recognized of these are the amyloid cascade hypothesis and tau hyperphosphorylation.

The amyloid cascade hypothesis proposes that the normal clearance mechanism of amyloid-beta (Aβ) in the brain tissue of AD patients is disrupted, leading to the accumulation of Aβ and the formation of Aβ plaque deposits[7]. The development of the amyloid cascade hypothesis can be seen in Fig. 1[8]. Aβ is a peptide produced by the proteolytic processing of amyloid precursor protein by β-secretase or γ-secretase[9]. The accumulation of Aβ triggers a series of neurodegenerative processes, such as inflammation, oxidative stress, and accumulation of tau protein, ultimately leading to symptoms of dementia. The formation process of Aβ plaque deposits can be referred to in Fig. 2[10]. Research into the amyloid cascade hypothesis has stimulated the development of several potential treatment strategies for AD. Examples include immunotherapies designed to clear Aβ plaques from the brain, and targeted β-secretase inhibitors[11]. Tau is a phosphoprotein that binds to and stabilizes microtubules. Hyperphosphorylation will lead to a decrease in the affinity of tau protein to microtubules, forming neurofibrillary tangles and depositing them in the cytoplasm, and no longer play the role of maintaining cell structure[12]. Factors including brain injury, hyperactivity of the TOR pathway, mutations in the tau gene, and metabolic syndrome can contribute to the formation of pathogenic tau. Certain pharmacological interventions, such as tau-directed monoclonal antibodies like ABBV-8E12, are designed to target tau protein and have been shown to reduce its levels in cerebrospinal fluid (CSF)[13].

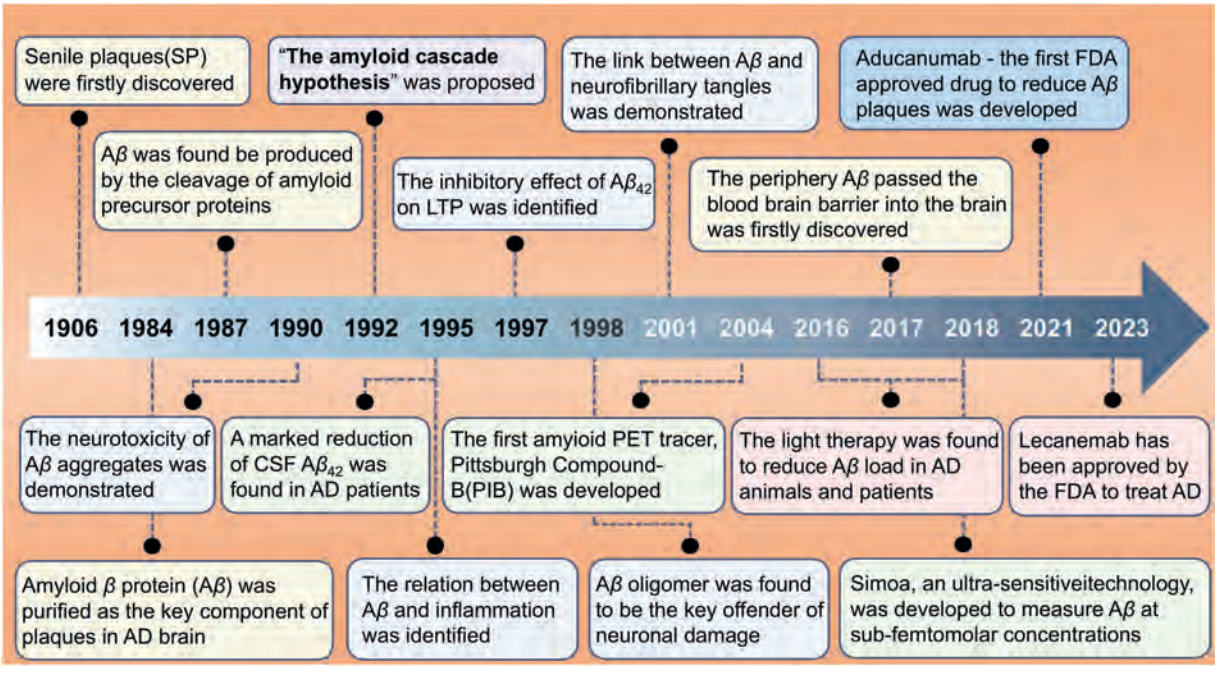

Figure 1 Milestone of the amyloid cascade hypothesis and its applications. Yellow box: key research findings; blue box: the amyloid-beta (Aβ)-related toxicity; green box: the diagnostic application; pink box: important drug and non-drug anti-Aβ therapies. Adapted with the permission of Ref. 8. Copyright © Signal Transduction and Targeted Therapy, 2023.

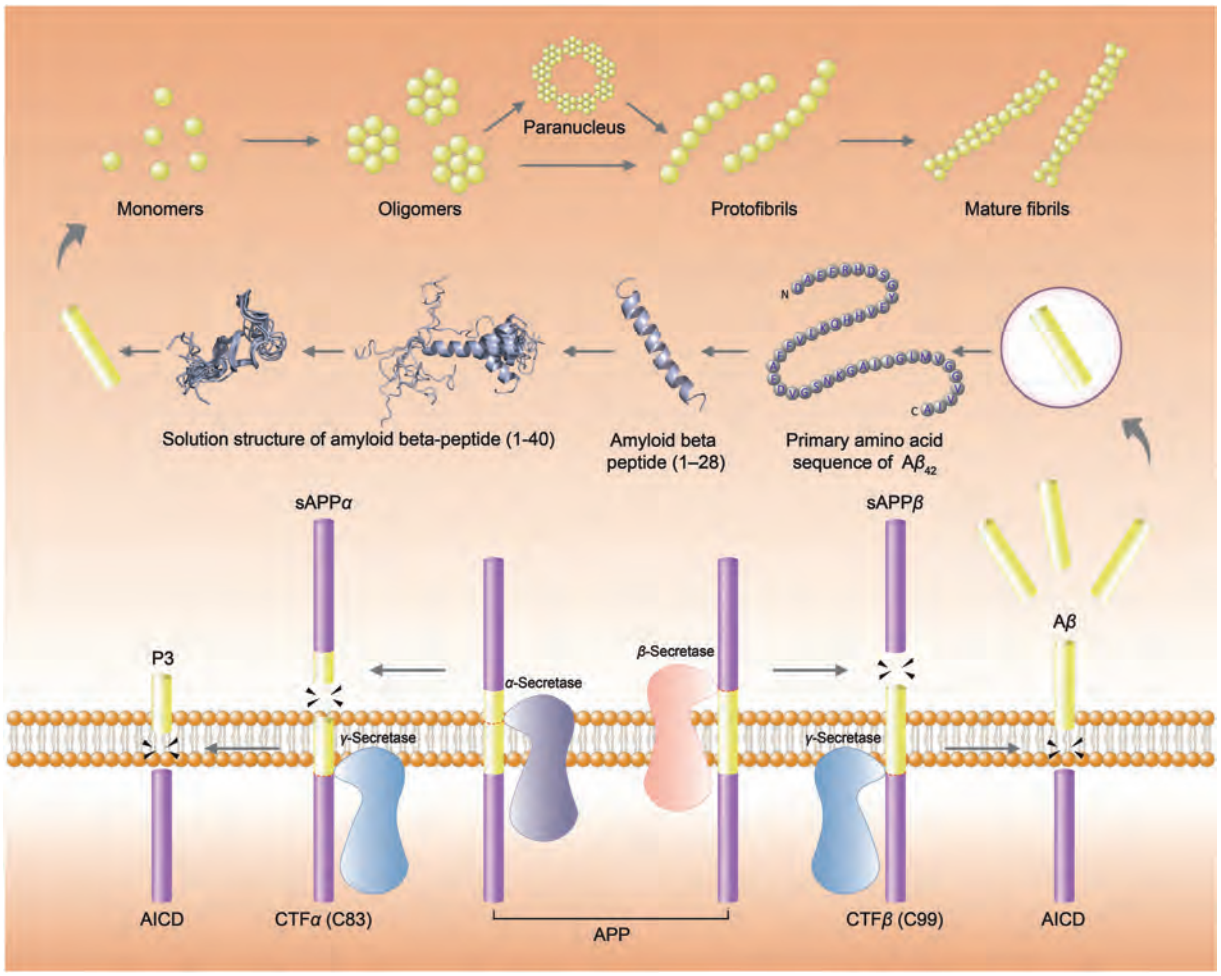

Figure 2 Human *APP* proteolytic pathways and structures of amyloid-beta (Aβ) monomer, fibril, and oligomers. Human *APP* proteolysis in the non-amyloidogenic pathway and the amyloidogenic pathway. The purple areas in the upper part of the figure, following the arrows, are the structure of Aβ (1−28), the solution structure of Aβ (1−40), and Aβ (10−35) forming a collapsed coil structure. At the top of the figure is a proposed pathway for the conversion of Aβ monomers to higher-order oligomers, protofibrils, and fibrils. Adapted with the permission of Ref. 10.

1.2. Artificial intelligence, computational biology, and systems biology

With the paradigm shift in the conceptualization of medical science and research, AD research may currently be undergoing a transformational phase. Emerging interdisciplinary fields such as artificial intelligence (AI), computational biology (CB), and systems biology (SB) are poised to be utilized in conjunction with multiple databases and molecular biological interactions to investigate the pathophysiology, diagnostic methodologies, and therapeutic approaches for AD.

AI, also known as machine intelligence, is a broad interdisciplinary field rooted in logic, statistics, cognitive psychology, decision theory, neuroscience, linguistics, cybernetics, and computer engineering that involves the known as the computational understanding of intelligent behavior, and the creation of artifacts that exhibit this behavior[14]. The history of AI can be seen in Fig. 3. AI systems analyze complex datasets utilizing specific algorithms, engage in continuous experiential learning, and employ statistical as well as machine learning (ML) techniques to evaluate model performance[15]. It has become a key driving force in the transformation of traditional medicine into precision medicine, and has been shown in multiple AD fields. It has good application prospects[16,17], see Fig. 4.

CB is an interdisciplinary subject of biology and computer science. It uses theoretical analysis, mathematical modeling, and computer simulation to analyze and understand biological problems. It can be used to identify coding regions representing proteins in genome sequences and decipher the codes hidden in nucleic acid sequences and genetic language rules[18,19]. CB is also a very interdisciplinary subject. On the one hand, it is the intersection of biological knowledge and AI, and on the other hand, it is the intersection of dry experiments and wet experiments. The application of AI in CB has led to significant breakthroughs in fields as diverse as genomics, medical diagnostics, and drug discovery. The pathological mechanism of AD involves the interaction of multiple genes and proteins and multi-scale physiological processes. CB can be integrated with SB to conduct a comprehensive analysis of AD genomics, transcriptomics, proteomics, metabolomics, radiomics, and other related fields. Essential information is extracted from the omics data, enabling the construction of a mathematical model that

Figure 3 Development of artificial intelligence (AI). It includes the presentation of some important concepts and the invention of algorithms and other technical achievements.

reflects the disease state. This approach elucidates the potential roles of disease-associated genes, proteins, and metabolic pathways[20-22]. CB can employ data analysis and theoretical methodologies, alongside mathematical modeling and computational simulations, to enhance the comprehension of the intricate nature of the progressing AD. This approach facilitates the exploration of novel mechanisms underlying AD and enables the prediction of functional pathways for newly identified pharmacological agents.

SB is an interdisciplinary field. The core concept is to reveal the complexity of life by integrating multidisciplinary knowledge, such as molecular biology, biochemistry, cell biology, genetics, physics, and mathematics, emphasizing the overall approach to study the global behavior of biological systems[23]. In AD, SB methods have been used to analyze the regulatory network of key processes such as neuroinflammation, oxidative stress, and energy metabolism, as well as the molecular mechanisms of abnormal accumulation of Aβ and tau proteins[24]. In addition, SB models are also used to evaluate the effects of drug interventions and predict treatment responses, thereby providing theoretical guidance for personalized treatment. With the continuous advancement of technology and the accumulation of data, these emerging disciplines are expected to play a more critical role in the prevention and treatment of AD.

2. Application of artificial intelligence, computational biology, and systems biology in diagnosing Alzheimer's disease

In the research of AD, the application of AI, CB, and SB has become an important means to reveal the deep mechanisms of the

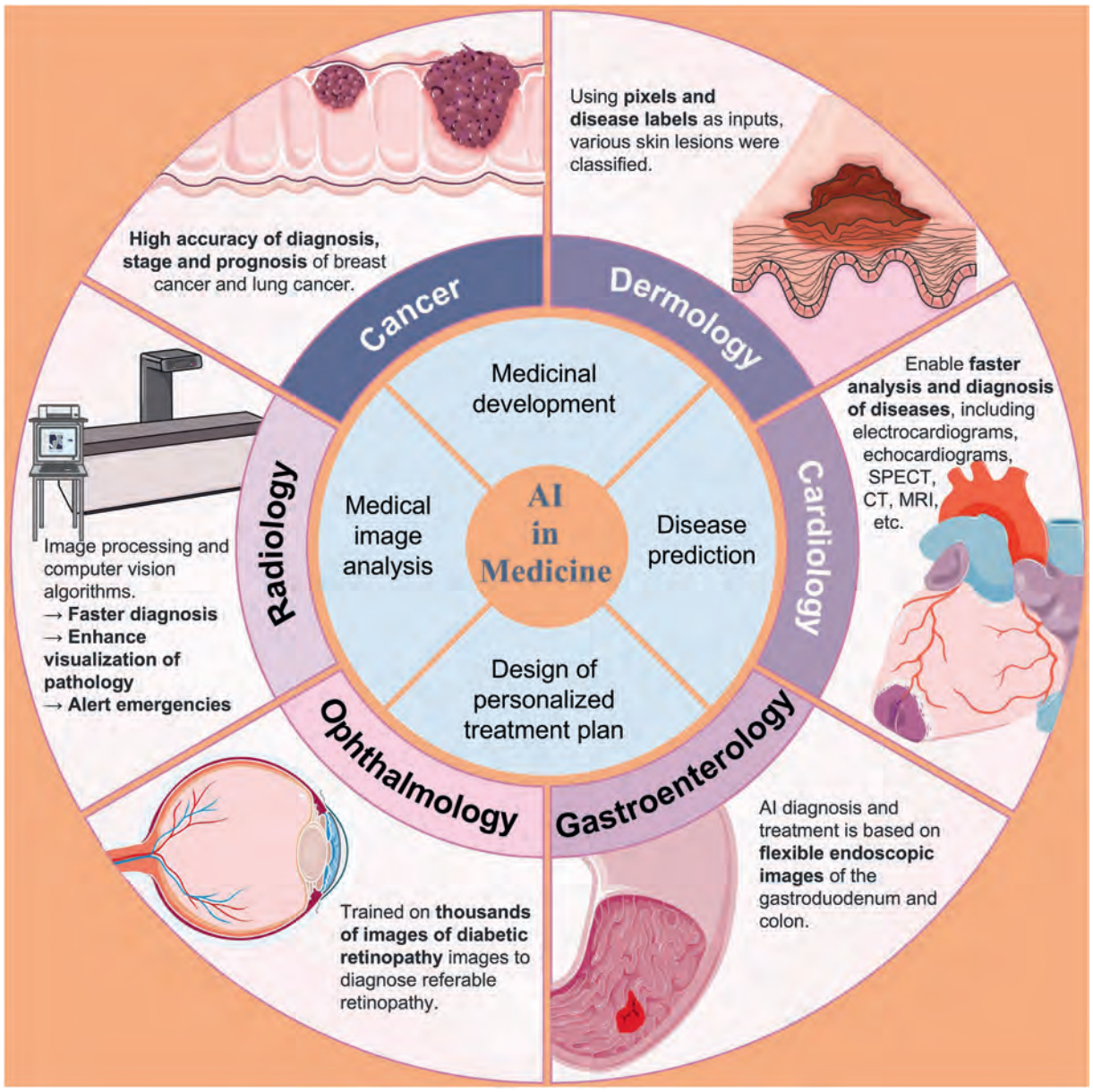

Figure 4 The application of artificial intelligence (AI) in the field of medicine. The range of applications of AI in the medical field is expanding, including medical image analysis, drug development, design of personalized treatment plans, disease prediction, and so on. AI shows promising applications in several medical specialties: radiology, oncology, dermatology, cardiology, gastroenterology, and ophthalmology.

disease, identify early AD risk factors, and develop treatment strategies.

2.1. Algorithms: machine learning and deep learning

A computer algorithm is an accurate and complete description of a problem-solving solution. It is a series of clear instructions for solving a problem. It represents a systematic method to describe the strategic mechanism for solving a problem. It is the basis for AI, CB, and SB to perform complex tasks. ML is a subset of computer algorithms capable of learning from provided data without requiring predefined inference rules, and has already found significant applications in medicine[25]. Deep learning (DL) is a subdiscipline of ML that relies on networks of simple interconnected units to generate increasingly advanced representations of the input provided. Specific algorithm representations of ML and DL can be seen in Fig. 5.

ML involves methods and algorithms that help learn and improve without requiring specific programming. It requires humans to identify and encode specific features based on data, runs on low-end machines with weak computing power, and can complete the work in seconds or hours[26]. Here, structured input data is divided into parts for analysis and then combined to represent the output. In ML, there are four commonly used learning methods: supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning[27]. Common algorithms include: linear regression, logistic regression, decision tree and random forest, support vector machine, K nearest neighbor, Bayesian classification, etc.

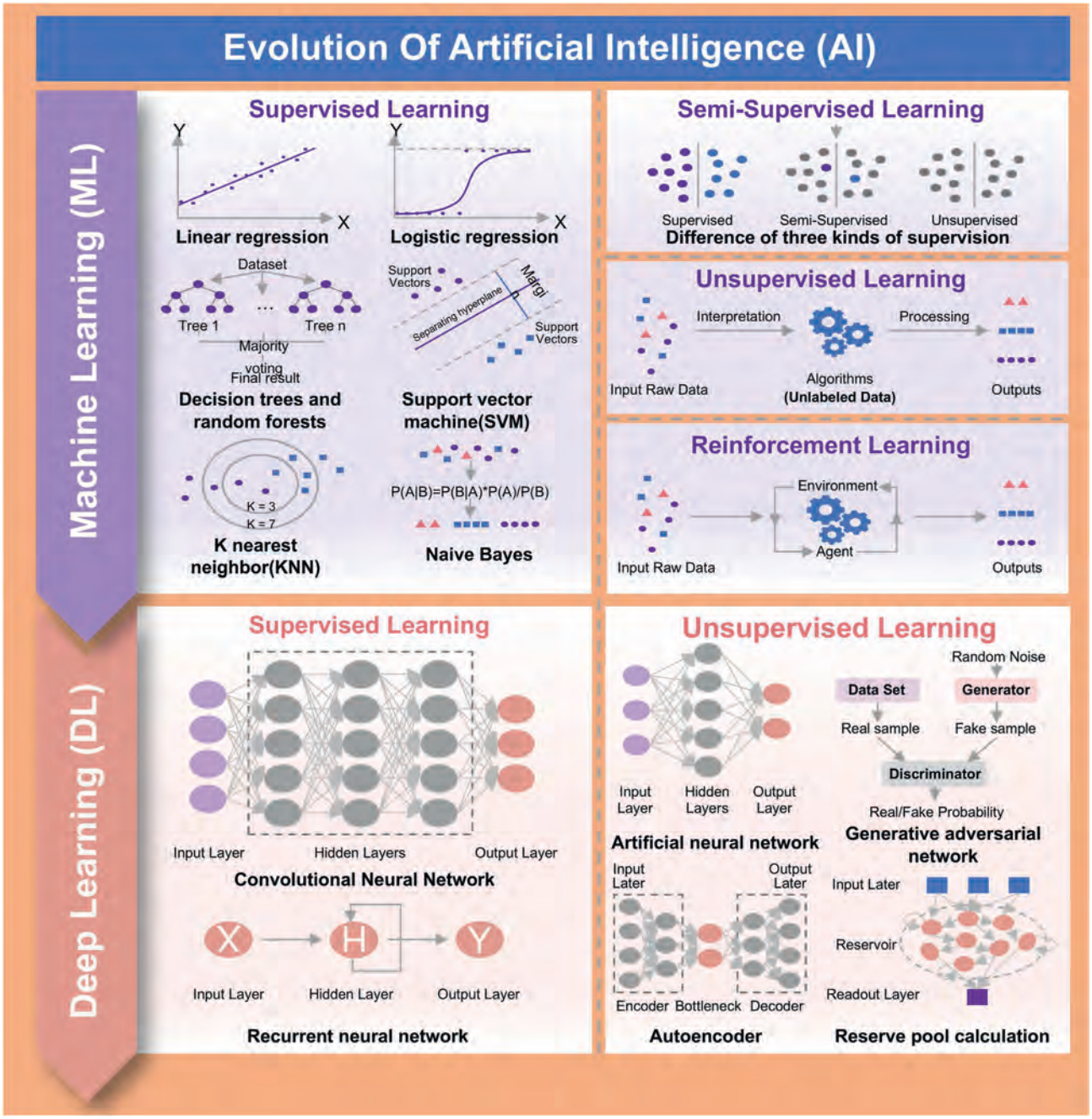

Figure 5 The evolution of artificial intelligence (AI): machine learning (ML) to deep learning (DL). In ML, there are four common learning methods, each useful for solving different tasks: supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning. Supervised learning includes six methods: linear regression, logistic regression, random tree and random forest, support vector machine, K-nearest neighbor, and naive Bayes. DL is a subset of ML that recognizes patterns using multiple processing layers of interconnected neurons between input and output layers, including two supervised learning methods of convolutional neural networks, recurrent neural networks, and four unsupervised learning methods of artificial neural networks, graph convolutional neural networks, autoencoder, and reservoir computing.

DL is a subset of ML that uses multiple processing layers of interconnected neurons between input and output layers to identify patterns. It is a complex ML algorithm that has achieved results far beyond speech and image recognition than previous related techniques[28]. The ultimate goal of DL is to enable machines to analyze and learn like humans, to recognize text, images, sounds, and other data, and to produce accurate predictions, including artificial neural networks, deep neural networks, convolutional neural networks, recurrent neural networks, graph convolutional neural networks, and other subgroups[26].

2.2. *Artificial intelligence identifies Alzheimer's disease risk groups*

AD is generally incurable and diagnosed late, and patients may benefit more from treatment if it is caught in the early stages,

before brain damage develops. Mild cognitive impairment (MCI) is a transitional state between normal aging and early AD. Among them, approximately 10%−15% of MCI patients have the possibility of converting to AD[29]. If MCI is diagnosed at an early stage, the incidence of AD can be reduced by nearly one-third through rehabilitation exercises and drug treatment[30,31]. Therefore, for effective treatment, MCI patients with high risk for AD must be detected, thereby delaying or preventing the transition from MCI to AD. However, early diagnosis of AD is a major challenge because subtle biomarker changes are often overlooked. DL has outstanding performance in detecting subtle and diffuse pathological abnormalities, and therefore has better application value in predicting MCI-AD conversion. For example, Ning et al.[32] and Zhou et al.[33] proposed a DL-based model to predict AD risk using genetic variation and neuroimaging data. Basaia et al.[34] used a convolutional neural network algorithm to predict the individual diagnosis of AD and the development of AD in MCI patients based on a single cross-sectional brain structural MRI scan. Jo et al.[35] used autoencoders to analyze neuroimaging data for the analysis and classification of AD, producing an AD classification accuracy of up to 98.8% and a prediction of 83.7% conversion from MCI to AD. However, the diversity of AD data and limited dataset size present additional challenges, mainly related to high dimensionality. Using the data set obtained from The National Alzheimer's Coordinating Center, Alatrany et al.[36] used support vector machine, SHAP, and LIME models to determine the risks of factors such as memory, judgment, commun, and orientation in AD, and successfully predicted AD progress over a 4-year period. Wang et al.[37] collected structural magnetic resonance imaging, clinical evaluation, and genetic polymorphism data from MCI patients from the ADNI database. Through a DL model combining interaction effects and multimodality, they achieved excellent results in predicting MCI conversion within 4 years (accuracy 92.92%; sensitivity, 88.89%; specificity, 95.33%). Zhou et al.[38] used data from ADNI and OASIS-brains databases, and used three convolutional neural networks (InceptionResNetv2, Densenet169, and SEResNet50), and used multi-task DL models and densely connected three-dimensional convolutional networks to realize automatic AD classification based on structured MRI imaging. Thus, by integrating multimodal data, AI models can capture a wider range of AD-related information, which can predict AD progress more accurately and longer-term and discover hidden patterns and biomarker correlations.

Aβ and tau are powerful biomarkers for identifying early AD and can be detected decades before symptoms appear[39,40], see Fig. 6[41]. For example, Aβ_{42} appears abnormal 18 years before a definite diagnosis, earlier than the appearance of clinical symptoms, and therefore becomes an indicator for early identification of AD patients. Aβ_{42} and Aβ_{40} are considered the most important isoforms of Aβ, and they have significant differences in metabolism, physiological functions, toxicity, and aggregation mechanisms. The ratio of Aβ_{42} to Aβ_{40} is abnormal 14 years before diagnosis and can be used to predict the future risk of AD. Abnormal p-tau and total tau protein levels appear approximately 10 years before diagnosis, earlier than hippocampal atrophy and cognitive decline, and represent an important direction for early identification of AD patients[41]. The reduction in hippocampal volume frequently manifests approximately eight years before the definitive diagnosis of AD, while cognitive decline typically emerges around six years before the onset of the condition.

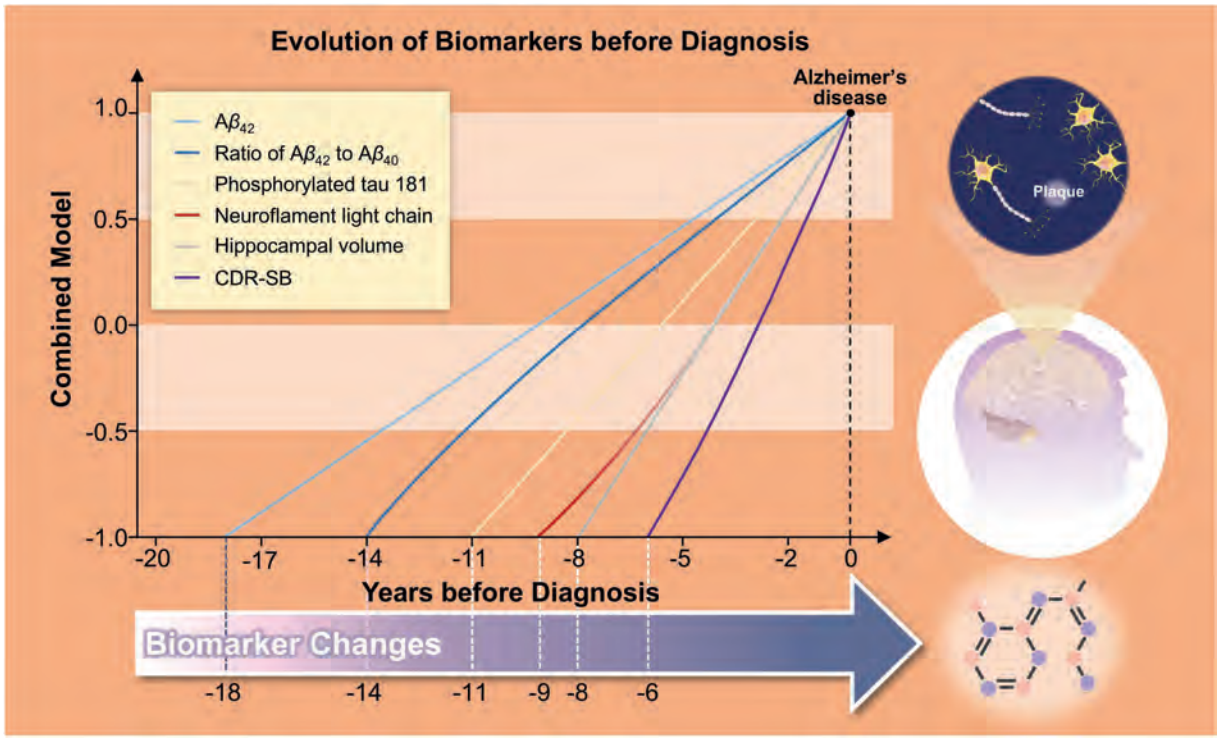

Figure 6 Evolution of Biomarkers before Diagnosis. During a median follow-up of 19.9 years, levels of cerebrospinal fluid (CSF) and imaging biomarkers in the Alzheimer's disease (AD) group diverged from those in the cognitively normal group at the following estimated numbers of years before diagnosis: Aβ_{42} at 18 years, the ratio of Aβ_{42} to Aβ_{40} at 14 years, phosphorylated tau 181 at 11 years, total tau at 10 years, neurofilament light chain at 9 years, and hippocampal volume at 8 years. Diagnoses of cognitive decline diverged at 6 years before formal diagnosis of AD. Adapted with the permission of Ref. 41. Copyright © 2024 The New England Journal of Medicine.

In addition to the two biomarkers Aβ and tau, researchers have also proposed other theoretical hypotheses and used other molecules as marker candidates. For example, D-glutamate levels are related to cognitive function in patients with AD or MCI[42]. Chang et al. used four ML algorithms (support vector machine, logistic regression, random forest, and naive Bayes) to build the best prediction model to distinguish MCI or AD patients from healthy controls, where the naive Bayes model and the random forest model are the best models to determine the susceptibility to MCI and AD, respectively. It is found that peripheral plasma D-glutamate levels are related to cognitive impairment and may be a suitable peripheral biomarker for detecting MCI and AD[43]. Formaldehyde (FA) is a possible by-product of several metabolic reactions (*e.g.*, methanol oxidation, DNA or histone demethylation), and relatively high FA concentrations have been detected in the brains of healthy adult mice, rats, and humans[44]. Clinical studies have shown that FA levels in urine, blood, and hippocampal anatomical samples of 141 AD patients were significantly higher than those of 38 age-matched controls[44,45]. In particular, urinary FA levels are positively correlated with the degree of dementia in AD patients, suggesting that FA may be used as a novel biomarker for the diagnosis of AD.

2.3. *Computational biology explores new mechanisms of Alzheimer's disease*

FA is a neuromodulator similar to NO. Studies have found that elevated FA concentrations are related to oxidative stress, energy disorders, and calcium overload, and may play a key role in various hypotheses of AD[46]. We have previously reported that FA abnormally accumulates in the brains of AD patients and AD animals. FA has also been found to promote Aβ_{40} aggregation *in vitro*[45,47]. Specific studies have found that in AD patients, there is a vicious cycle between Aβ assembly and FA production. On the one hand, Aβ accelerates the accumulation of FA by inactivating formaldehyde dehydrogenase (FDH); on the other hand, FA promotes Aβ oligomerization and fibrosis. Tremor and tau hyperphosphorylation[48]. It is known that Aβ dimers induce neuronal dysfunction in early AD and provide "seeds and nuclear structures" for the formation of Aβ oligomers and fibrils in late AD. CB molecular simulations found that FA interacts with the β-spin of Aβ monomers. Cross-linking of K28 (lysine, K) residues on Aβ promotes the formation of Aβ dimers, oligomers, and fibrils. Mutation of Aβ_{42} on the K28 residue or depletion of FA completely abolished Aβ aggregation[49]. Animal experiments also confirmed that FA injection indeed enhanced the formation of intracellular Aβ oligomers and extracellular senile plaques in *App/Ps1* mice through $NaHSO_3$ (an exogenous FA scavenger) and Q10 (an exogenous FA scavenger). Endogenous FA scavengers can reduce Aβ oligomers and senile plaques and restore memory function in *App/Ps1* mice[48]. The specific mechanism can be seen in Fig. 7[50].

Endogenous FA is metabolized and utilized in the body by participating in the "single carbon cycle" or by FA-related enzymes, and is mainly degraded by glutathione-dependent FDH (also known as mouse ADH3, human ADH5)[51]. FDH is strongly

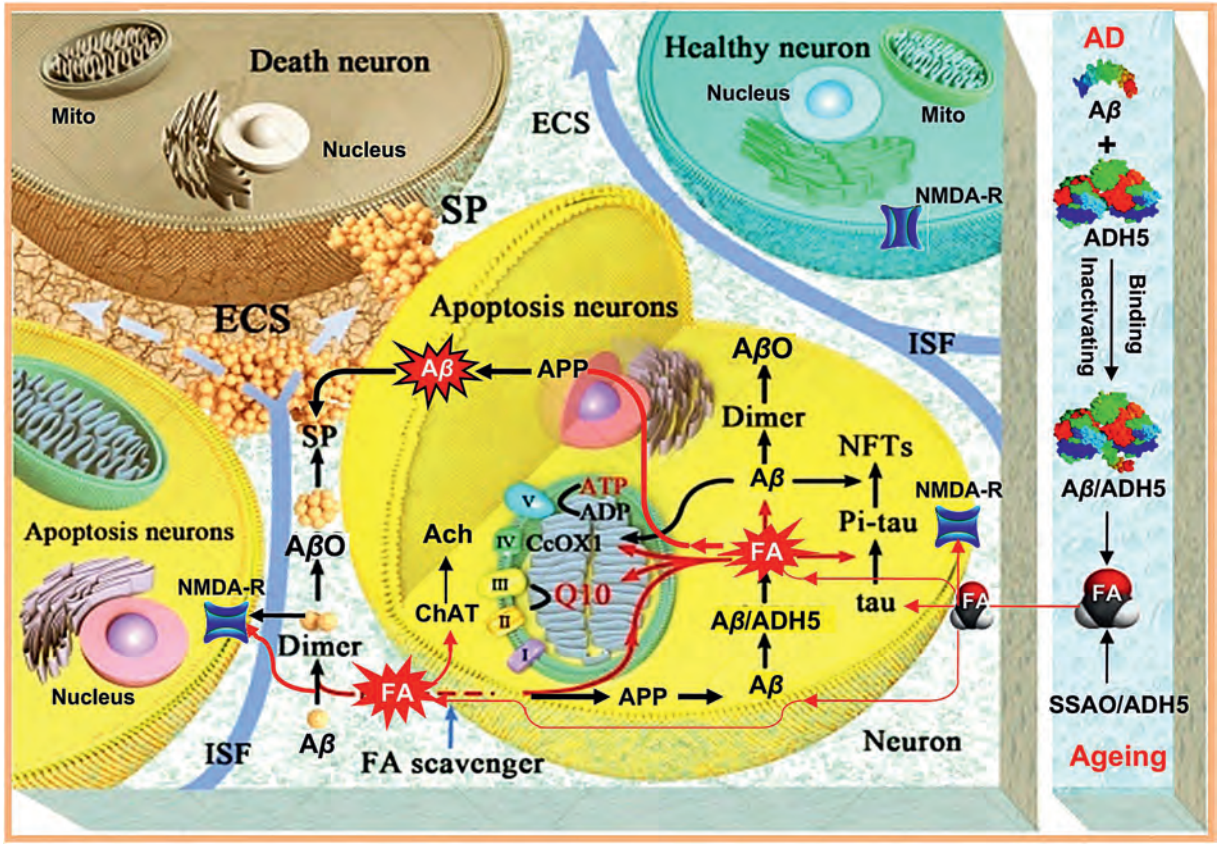

Figure 7 Aβ deposition in extracellular spaces (ECS) blocks interstitial fluid (ISF) flow and drug delivery into the neurons in the deep layer of the cortex. Reproduced with the permission of Ref. 50. Copyright © 2024 International Journal of Biological Macromolecules.

expressed in white matter and moderately expressed in gray matter, and can functionally degrade FA rapidly[52]. Studies have found that aging causes the expression and activity of FDA to decrease, while SSAO (an FA-generating enzyme) increases. Compared with 4-month-old AD mice, FDH activity is significantly reduced in 6-month-old AD mice, thus leading to FA accumulation. Higher FA levels are associated with more Aβ in the brain[53].

Recent studies have found that Aβ_{42} can bind to human ADH5 and induce structural changes in ADH5, leading to its inactivation, thereby causing FA accumulation in the brain. Theoretically, the first residue of Aβ_{42}, aspartic acid (D1), is connected to the 96th residue of ADH5, glutamine (Q96). Through CB molecular simulation, the 97th residue of ADH5-Cysteine (C97 in structure Zn^{2+}) is linked[49]. In order to verify the above speculation, Yue et al.[53] simulated the structure of Aβ_{42} binding to ADH5. The three-dimensional crystal structure of ADH5 shows that the cysteine 45 (CYS45) residue is bound to the catalytic Zn21, and the CYS97, CYS100, CYS103, and CYS111 residues are linked to the structural Zn21. Simulated Aβ_{42}−hFDH complex shows hydrogen bond formation between ASP1 of Aβ_{42} (D, yellow) and GLN96 of ADH5 (Q, purple). GLN96 is connected to CYS97/CYS100 of ADH5. The results show that Aβ_{42} binds to GLN96, resulting in the formation of a disulfide bond (SS) between CYS97 and CYS100. To verify the simulation results, Yue et al.[54] extracted and purified ADH5. Through liquid chromatography-tandem mass spectrometry analysis, it was found that Aβ_{42} increased the SS bond formation between CYS97 and CYS100 by 1.4%, while reducing the SS bond formation between CYS103 and CSY111 by 5.9%. CYS111 is linked to catalytic ARG115, which is critical for ADH5 activity. These data suggest that Aβ_{42} induces cleavage of the SS bond between CYS103 and CSY111, leading to the dissociation of catalytic ARG115 and thus inactivation of ADH5. Further evidence shows that Aβ also decomposes active tetrameric ADH5 to form inactive dimer ADH5, resulting in reduced ADH5 activity and increased intracellular FA levels in cultured cells and *App/Ps1* mice, as shown in Fig. 8[49,53].

2.4. *Systems biology improves Alzheimer's disease diagnosis*

AD is heterogeneous and multifactorial in nature. In the AD brain, multiple molecular pathways and intracellular signaling are dysregulated and are highly interconnected through genetic and cross-talk interactions[55]. Therefore, a holistic, systems-level approach is needed to fully capture the multifaceted pathophysiology of AD[56]. SB can integrate multi-scale and multi-omics data, build dynamic models, and explore molecular interactions and network regulation in disease states. It is particularly suitable for AD diagnosis in an interdisciplinary model. Here, we divide the diagnosis of AD into two steps: detection and evaluation, as seen in Table 1.

The detection of AD patients is divided into two aspects: biomarkers and imaging. Biomarker data will help detect and map changes in the upstream pathological mechanisms of AD and the downstream molecular effects that occur in the preclinical stage. Neuroimaging data will identify multidimensional biological signatures at the subpopulation or even individual level that are critical for tracking clinical biology trajectories. Studies have shown that AD is associated with reduced CSF Aβ_{42} and increased tau isoforms[57]. The decrease in CSF Aβ_{42} levels reflects the increased aggregation and deposition of Aβ in the brain[57]. The increase in CSF p-tau and t-tau directly reflects the aggregation of tau in the brain and neurodegeneration[57]. In addition to CSF, considerable efforts have been made over the past decade to identify blood-based biomarkers. Currently, only a limited number of approved blood-based tests are available for detecting AD pathology. For example, plasma p-tau181 and p-tau217 have been shown to distinguish AD from other neurodegenerative diseases and predict cognitive decline in AD patients[58-60]. Imaging examinations include conventional MRI, which is helpful to evaluate the degree of brain atrophy and rule out non-AD causes, including vascular dementia, frontotemporal atrophy, asymmetric frontoparietal atrophy, etc. Among them, fMRI can accurately diagnose AD and predict the early stages of the disease[61]; dMRI can study the changes in white matter microstructure in AD[62]; PET can reveal the metabolism of AD patients in the early stages[63]. With the development of DL, combining structural imaging and functional imaging with DL can improve the accuracy of diagnosis. For example, Warren et al.[64] found that using various types of default mode networks can diagnose different stages of AD with high accuracy, improve diagnostic accuracy, and simplify fMRI analysis. Ruan et al.[65] obtained the high sensitivity and specificity of amyloid-PET in diagnosing AD based on the Bayesian random effects model.

When a patient initially presents with symptoms consistent with the early stages of AD, clinicians must perform a thorough clinical evaluation to rule out other potential non-AD causes of cognitive impairment. Clinical assessment includes cognitive assessment, functional assessment, and medical history assessment. Qiu et al.[66] developed a new DL framework that links fully convolutional networks with traditional multilayer perceptrons to depict unique AD characteristics from multimodal inputs of MRI, age, gender, and simple mental state examination scores to generate high-resolution visualization of AD risk, which can then be used to accurately predict AD status. Later, Qiu et al.[67] developed a DL model that includes demographics, medical history, neuropsychological testing, neuroimaging, and functional assessment, which can accurately classify subjects of normal control, MCI, and AD in multiple cohorts of participants with different causes of dementia and different levels of cognitive function. And applying an interpretability method in computer vision, demonstrating that this model can track different patterns of degenerative changes throughout the brain. In addition to routine medical history, neuropsychological tests, neuroimaging, and functional assessments, genomics, epigenomics, metagenomics, transcriptomics, microRNAomics, proteomics, and metabolomics/lipomics play an increasingly important role in the study of AD[56]. Recently, SB has identified numerous AD-related genes through network and pathway-based methodologies. For instance, integrating AD risk loci with the single-nucleus assay for transposase-accessible chromatin using sequencing (snATAC-seq) database can associate specific cell types and delineate *cis*-regulatory chromatin accessibility networks[68]. Previous studies have elucidated the potential *cis*-regulatory interactions involving *BIN1*, *ADAM10*, *APOE*, and *SCL24A4* by integrating cooperative accessibility maps with chromatin accessibility data and genome-wide association study statistics across the genomic axis. Their findings highlighted *APOE* as a significant contributor to the heritability factors associated with AD. Additionally, SB approaches can facilitate the development of computational models of gene regulation in the form of networks, which map interactions between transcription factors and their potential target genes. This methodology has unveiled the connections between disease and protein interactions, identified novel pathological processes implicated in AD, and offered innovative perspectives

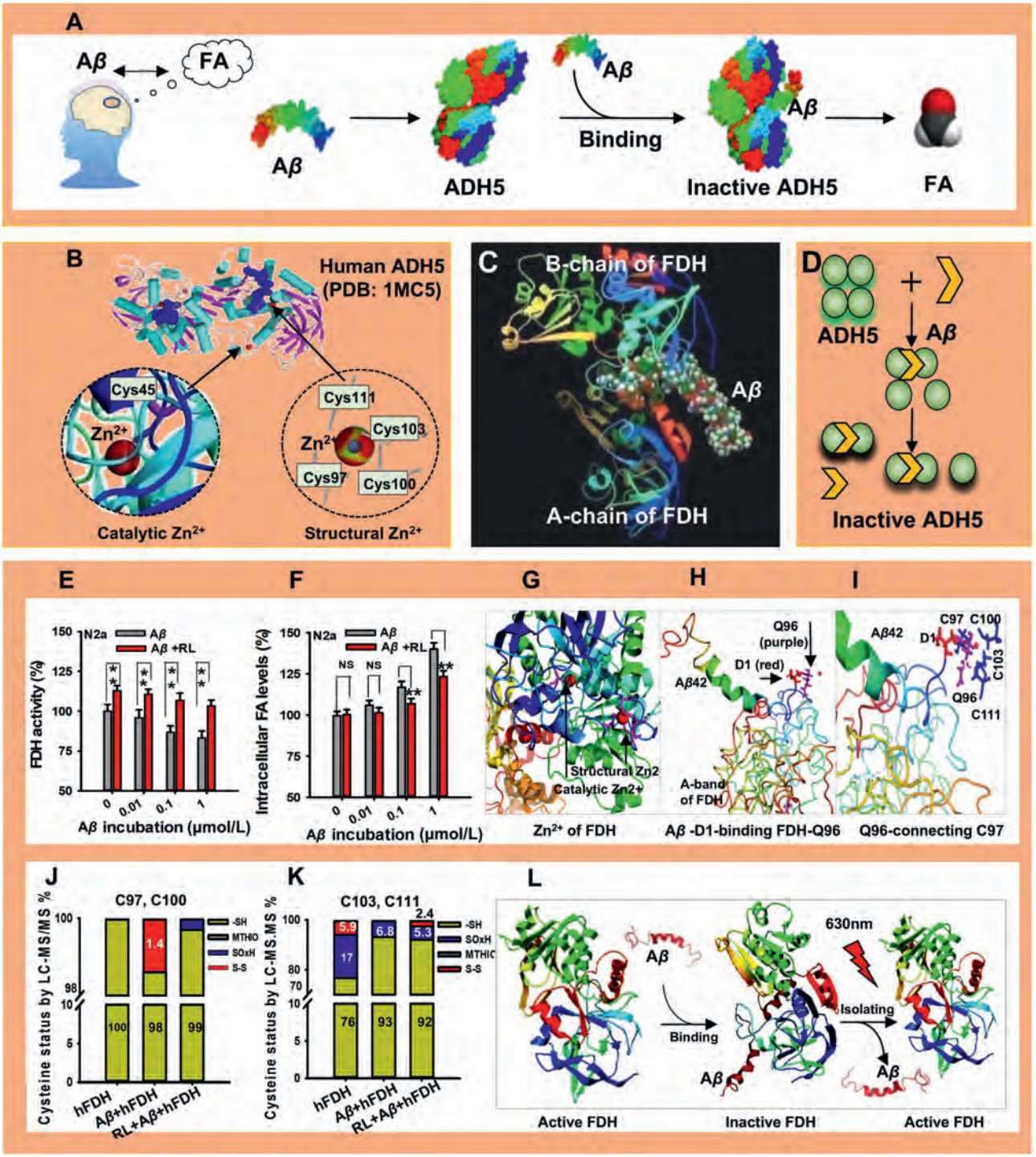

Figure 8 Aβ-binding with ADH5 induces formaldehyde (FA) accumulation. (A) The model of Aβ-induced FA accumulation by inactivating ADH5. (B) The crystal structure of human ADH5 (PDB: 1MC5) contains catalytic Zn^{2+} and structural Zn^{2+}. (C) Aβ binds with the A and B chains of ADH5 by molecular simulation. (D) Aβ disassembles the active tetramer ADH5 to form the inactive dimer of ADH5. (E) Quantitative assessment of FDH activity in the cultured N2a cells analyzed by ELISA. (F) Quantitative results of intracellular FA content detected by HPLC. (G) The crystal structure of cysteine residues binding with catalytic and structural Zn^{2+} (PDB: 1M5C). (H) ASP1 (D, yellow) residue of $Aβ_{42}$ was connected with the GLN96 (Q, purple) residue of hFDH, simulated by molecular simulation. (I) $Aβ_{42}$-induced model of disulfide bond formation between CYS97 and CYS100 residues of hFDH. (J, K) Quantitative assessment of the modification in CYS97, CYS100, and CYS111 of hFDH detected by liquid chromatography−tandem mass spectrometry (LC−MS/MS). (L) The model of LED-RL disassembly of the Ab/FDH complex. Reproduced with the permission of Ref. 49. Copyright © Ageing Research Reviews, 2022 and Ref. 53. Copyright © 2019 Alzheimer's & dementia (New York, NY, USA).

Table 1 Application of artificial intelligence (AI), computational biology (CB), and systems biology (SB) in diagnosing Alzheimer's disease (AD).

AI identifies people at risk of AD			
Data type		Tool	Significance of application
Multimodal neuroimaging data	MRI imaging of medial temporal lobe volume loss	Linear discriminant analysis (LDA)	Important biomarkers for assessing progression to AD in patients with MCI.
	PET imaging of amyloid	Random subset feature selection algorithm (RSFS)	Satisfactory accuracy in distinguishing AD patients from normal control patients and in predicting conversion of MCI to AD dementia.
	Single cross-sectional MRI scan of brain structures	Convolutional neural network (CNN)	Predicting individual diagnosis of AD and development of AD in MCI patients.
Biochemical marker	D-Glutamic acid	Support vector machines, logistic regression, random forest, and plain Bayes	Peripheral plasma D-glutamate levels correlate with cognitive impairment and may be a suitable peripheral biomarker for detecting MCI and AD.
CB explores new mechanisms of AD			
Tool	Significance of application		
Molecular simulation in CB	Cross-linking of FA with the K28 (lysine, K) residue on the β-spin of the Aβ monomer was found to promote the formation of Aβ dimers, oligomers, and protofibers. The 97th residue-cysteine (C97 in structure Zn^{2+}) of ADH5 was found to be connected.		
SB refines AD diagnosis			
Methodologies		Significance of application	
Identification of many AD-related genes using network- and pathway-based approaches		Combining AD risk loci with the snATAC-seq database allows linking specific cell types and defining *cis*-regulated chromatin accessibility networks Overlaying synergistic accessibility maps with chromatin accessibility signals and GWAS statistics along the genome axis revealed a potential *cis*-regulatory relationship between BIN1, ADAM10, APOE, and SCL24A4, and APOE was found to be a major determinant of AD heritability	
Generating computational models of gene regulation in the form of networks		Mapping the interactions between transcription factors and their potential target genes, revealing the link between disease and protein interactions, and discovering new abnormal processes involved in AD.	

for the diagnosis of the disease[56,69,70]. Although there are several studies on the diagnosis and biomarker recognition of AD, studies involving the optimization of treatment options for AD patients are lacking. Bhattarai et al.[71] proposed a reinforcement learning-based model to study the best AD treatment plan based on electronic health records. They used model-free Q-learning and model-based policy iteration to generate program plans, providing strong guidance for AD treatment plans.

3. Application in Alzheimer's disease drug research and development

A major challenge in AD treatment is in the field of drug discovery, with only five drugs approved to date. Four of them are acetylcholinesterase inhibitors: donepezil, galantamine, rivastigmine, and tacrine, and the other one is an NMDAR antagonist: memantine. Most therapeutic drugs target amyloid, tau protein, mitochondrial dysfunction, oxidative stress, metal imbalance, neuroinflammation, etc., but they are unable to prevent and restore disease progression, see Fig. 9[72]. Therefore, there is an urgent need for new drug targets and drug compounds to alleviate symptoms and lesions of the central nervous system[73]. However, low efficacy, off-target delivery, time-consuming, and high cost are obstacles and challenges affecting drug design and discovery.

In addition, complex big data from genomics, proteomics, microarray data, and clinical trials also pose obstacles to drug discovery[74]. SB can investigate biological processes through the application of network theory, elucidating the interconnections among individual molecules, such as DNA−protein, RNA−protein, protein−protein, and protein−metabolite networks-within structurally and functionally organized networks and systems in both healthy and AD populations[56]. CB can automate feature extraction from big data through DL, analyze literature and high-throughput compound screening data, and propose plans for initial molecular screening and automated chemical synthesis. Once the bioassay data is obtained, by updating the DL model, a new molecular optimization plan can be proposed, and the bioassay can be performed again. In this way, an automated drug development cycle based on AI design and high-throughput bioassays is formed. The specific content can be seen in Fig. 10.

3.1. Drug discovery

The primary approach to drug discovery is to develop drugs (small molecules, peptides, antibodies, or new modalities including RNA or cell therapies) that modify disease states by modulating the activity of molecular targets.

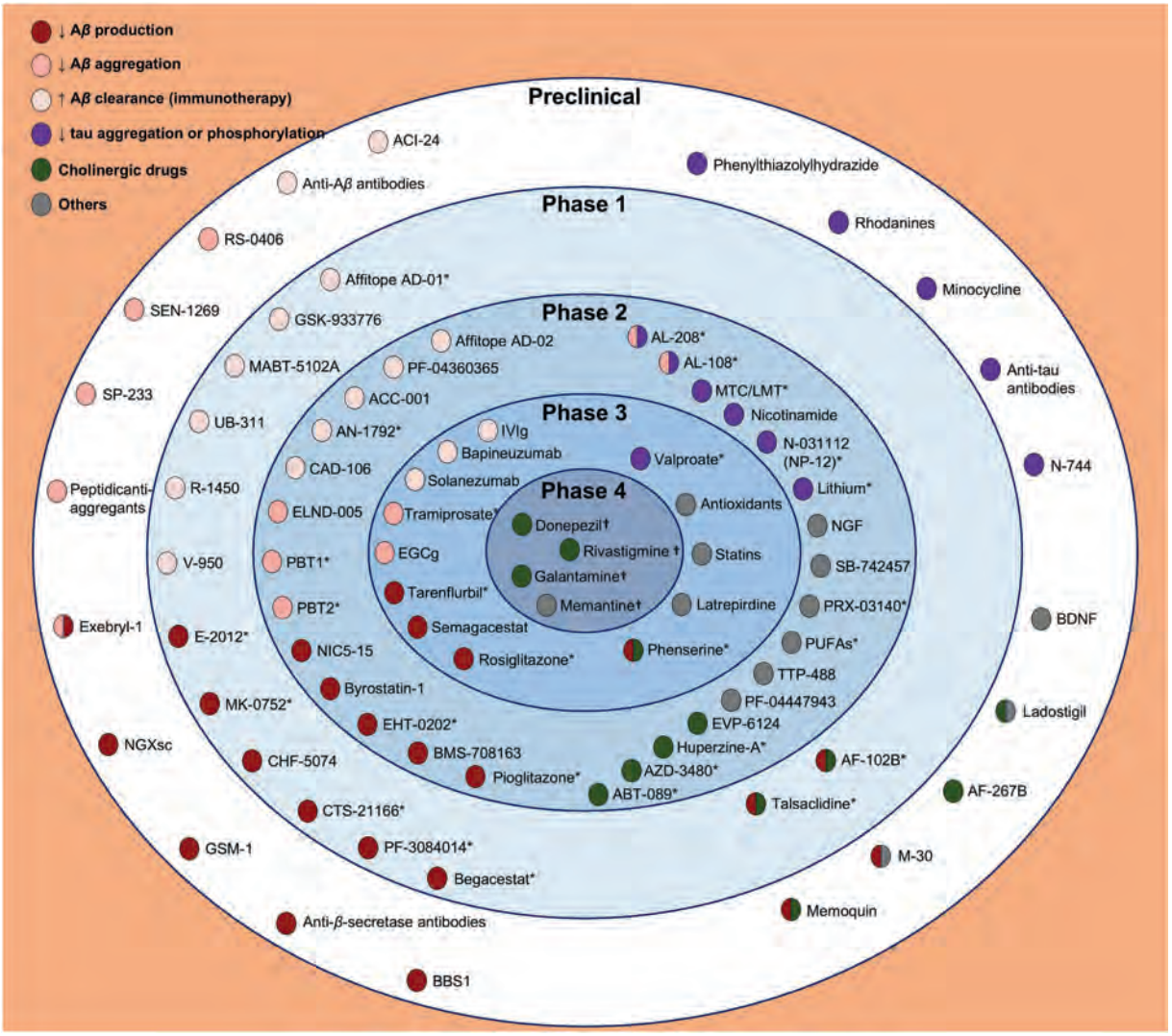

Figure 9 Drug development in Alzheimer's disease (AD). Drugs being investigated for AD therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies *in vitro* and animal models). *RCTs in AD are not ongoing. †Drugs approved for the treatment of AD. Adapted with the permission of Ref. 72. Copyright © 2010 The Lancet Neurology.

3.1.1. Related model - Quantitative structure−activity relationship

In drug design and development, it is crucial to study the relationship between the chemical structure of a drug, its physicochemical properties, and biological activity. Establishing mathematical models can identify different chemical structures from molecular databases as targets for disease treatment. For example, SNF-CVAE, based on drug similarity network fusion, identified promising therapeutic drugs for AD and juvenile rheumatoid arthritis[75]. Zang et al.[76] 2019 developed a DL-based model, called deepDR, to predict approved drugs such as risperidone and aripiprazole for the treatment of AD. We will introduce the most basic and commonly used mathematical model in the field of drug discovery: Quantitative Structure−Activity Relationship (QSAR). QSAR is one of the most important tools in computer-aided drug design. It uses mathematical methods to construct a quantitative mapping relationship between chemical structures and their biological activities. It can automatically screen molecular databases with diverse structures and synthesize and test the most suitable compounds in the laboratory[77]. It is beneficial to save experimental resources, reduce the blindness of experiments, and speed up the development process. In 2016, Subramanian et al.[78] used a deep neural network with Canvas descriptors to build classification and regression models to predict the binding affinity of human β-secretase 1 inhibitors. β-Secretase 1 inhibitors an aspartic protease that exists in the central nervous system. It can catalyze the first and critical step in the formation of the Aβ peptide. It is considered a key target for regulating cognitive impairment and treating AD. Experimental results show that the deep neural network model has good classification ability with an accuracy of 0.82, and good regression ability with a coefficient of determination of 0.74 and a mean absolute error of 0.52[78]. This shows that the DL-based QSAR model has good activity prediction performance.

3.1.2. Big data analysis

The term "big data" refers to massive data whose data structures are large, diverse, and complex, making it difficult to store,

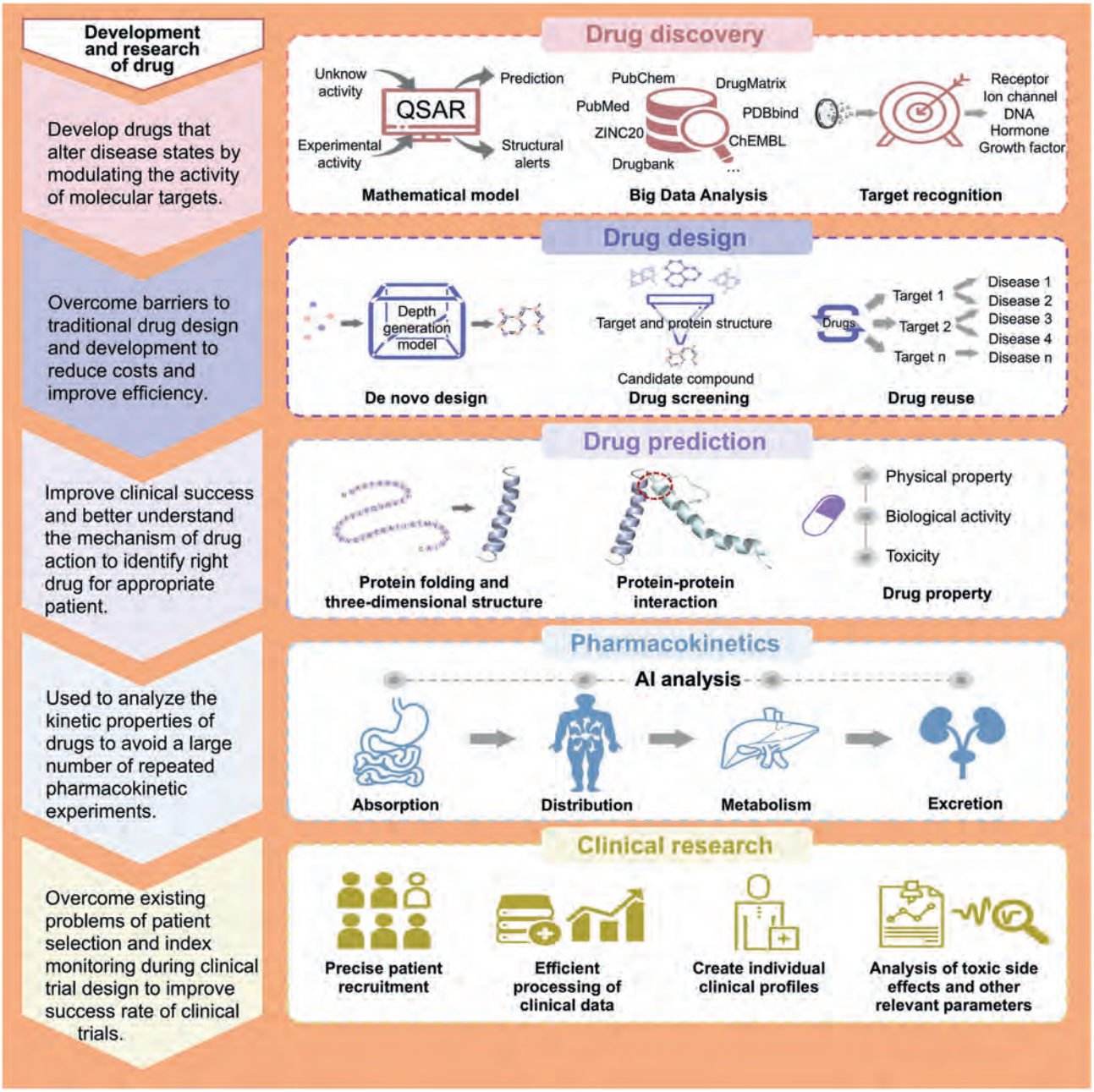

Figure 10 The role of artificial intelligence (AI) in Alzheimer's disease (AD) drug development.

analyze, and visualize them using traditional computing methods[79]. With the emergence of microarray, RNA-seq, and high-throughput sequencing technologies, large amounts of biomedical data are generated every day, and contemporary drug discovery has transitioned into the era of big data. In drug discovery, big data has "ten V" characteristics: volume, velocity, variety, veracity, validity, vocabulary, venue, visualization, volatility, and value[80]. With the increase in biological and chemical data in the literature and the development of *in vitro* and *in vivo* clinical studies, genomics studies, proteomics studies, metabolomics studies, and gene ontology studies, different databases have been developed. For example, PubMed, PubChem, ChEMBL, DrugBank, DrugMatrix, ZINC20, PDBbind, BindingDB, UniProt, ProteinDataBank, AlphaFold, etc, are essential databases for compound synthesis and screening in the drug design and discovery process. ADNl, OASlS, MlRlAD, AlBL, AlzData, NIAGADS, NCRAD, AlzGPS, TACA, ADKnowledgePortal, etc. are commonly used databases for AD target and drug discovery (Table 2[81]).

Developments in CB can help extract useful features, patterns, and structures present in these large biomedical data sets. By conducting random forest, classification and regression, neural network, and other analyses on the compounds in the database, combined with the QSAR model, molecular docking, and molecular dynamics simulation research can be carried out. For example, Chen et al. used data from the database and used DL and random forest algorithm prediction models to conclude that 3-*O*-feruloylquinoic acid methyl ester contained in boxwood and green

Table 2 A selected list of multi-Omics and bioinformatics/cheminformatics resources for Alzheimer's Disease (AD) drug discovery. Reproduced with the permission of Ref. 81. Copyright@ 2024 Current Opinion in Structural Biology.

Source	Description	Website
Multi-omics sources for AD drug discovery		
AD knowledge portal	Database of multi-omics related to AD, Dementia and aging, including genomic, transcriptomic, proteomic and metabolomics data from human and animals.	https://adknowledgeportal.synapse.org/
NIAGADS	Database of genetic, genomic, and phenotypic data for AD and AD-related dementia.	https://www.niagads.org/
NCRAD	Database of biological specimens for AD and AD-related dementia.	https://ncrad.iu.edu/
AlzGPS	Database of multi-omics, human protein interactome, disease module and drug repurposing for AD; analysis tools available.	https://alzgps.lerner.ccf.org/
TACA	Database of single-cell/single-nucleus RNA-seq data, ligand-receptor networks, protein interaction networks, drug-target networks and synapse.org/gene-eQTL/pQTL associations for AD; analysis tools are provided.	https://taca.lerner.ccf.org/
ADNI	Database of neuroimaging, biomarkers, genetic and clinical data for AD.	https://adni.loni.usc.edu/
Bioinformatics/cheminformatics sources for AD target and drug discovery		
ZINC20	Database of commercially available Compounds for virtual screening.	https://zinc20.docking.org/
PubChem	Database of chemical information.	https://pubchem.ncbi.nlm.nih.gov/
ChEMBL	Database of chemical, bioactivity and genomic data.	https://www.ebi.ac.uk/chembl/
DrugBank	Database of drugs, drug targets and clinical information.	https://go.drugbank.com/
PDBbind	Database of experimentally measured binding affinity data for complexes in the protein data Bank.	http://www.pdbbind.org.cn/
BindingDB	Database of binding affinities of protein-ligand complexes.	http://www.bindingdb.org
UniProt	Database of protein sequence and functional information.	https://www.uniprot.org/
Protein data Bank	Database of experimentally determined 3D structures.	https://www.rcsb.org/
AlphaFold protein Structure database	Database of AI-predicted protein 3D structures for a while proteome.	https://alphafold.ebi.ac.uk/

rutin A contained in Qingtong can form a stable interaction with GSK3β, thereby inhibiting the activity of GSK3β[82]. GSK3β is an enzyme related to AD. It participates in the pathogenesis of AD by regulating the abnormal aggregation of Aβ, tau protein phosphorylation, nerve cell apoptosis, and inflammatory response. Inhibiting the activity of GSK3β could serve as a target for developing AD drugs.

3.1.3. Target identification

The main goal of drug discovery is to produce a drug that can change the disease condition. As one of the most cutting-edge treatments for AD, targeted drug therapy has the advantages of high efficiency, few side effects, and low drug resistance in patients[83]. The discovery and confirmation of drug targets is the first step in targeted drug development. Drug targets are special sites formed by biological molecules to which drugs can bind to produce pharmacological effects (targeted agonists/inhibitors) to prevent and treat diseases. Based on the biological properties of biomolecules, drug targets can be divided into receptors, enzymes, ion channels, DNA, hormones, and growth factors. With the development of life sciences and bioinformatics, more and more target structures have been analyzed. For example, Tsuji et al.[84] developed a DL-based computational framework that can extract low-dimensional representations of high-dimensional protein interaction network data to infer potential drug target genes. Tsuji et al. successfully identified key genes that may serve as targets for treating AD (*e.g.*, *DLG4*, *EGFR*, *RAC1*, *SYK*, *PTK2B*, *SOCS1*) and deduced potential compounds for treating AD (*e.g.*, tamoxifen, bosutinib, and dasatinib). Pan et al.[85] developed an AI-based drug discovery network (AI-DrugNet), identified multiple potential AD drug combinations, and identified five AD therapeutic targets: *AGTR1*, *FEN1*, *NADSYN1*, *PDHB*, and *PSMB2*. Common potential targets for AD include Aβ, tau protein, apolipoproteins, lipid and lipoprotein receptors, neurotransmitter receptors, neurogenesis, inflammation, oxidative stress, cell death, proteostasis, bioenergetics and metabolism, vascular factors, growth factors and hormones, synaptic plasticity and neuroprotection, gut−brain axis, circadian rhythm, epigenetic regulators, etc.[86]. See Fig. 11 for details.

Currently, several clinical trials of drugs targeting brain Aβ plaques have been conducted for the treatment of AD, such as aducanumab, lecanemab, donanemab, gantenerumab, and ALZ-801[87]. These drugs are designed to reduce the amount of Aβ plaques in the brain or reduce the formation of Aβ plaques, thereby slowing or reversing cognitive decline in AD patients. Lecanemab (also known as BAN2401) is a humanized version of the mouse antibody mAb158. It is an immunoglobulin G1 monoclonal antibody that preferentially targets soluble Aβ fibrils and is active against insoluble fibrils[88] (Fig. 12). Phase III clinical trials showed that compared with the placebo group, the lecanemab group had a 27% reduction in dementia scores, a 26% reduction in cognitive loss, and reductions in amyloid, tau, neurodegeneration, and neuroinflammation markers. Another phase III trial of the anti-Aβ antibody gantenerumab has been shown to inhibit cognitive decline in patients with prodromal AD[89]. The emergence of targeted drugs will lead AD treatment into a new era of "cause-specific treament" and provide better treatment options for AD patients.

In addition to monoclonal antibodies, DNA aptamers are emerging as an alternative to AD immunotherapy. Aptamers are

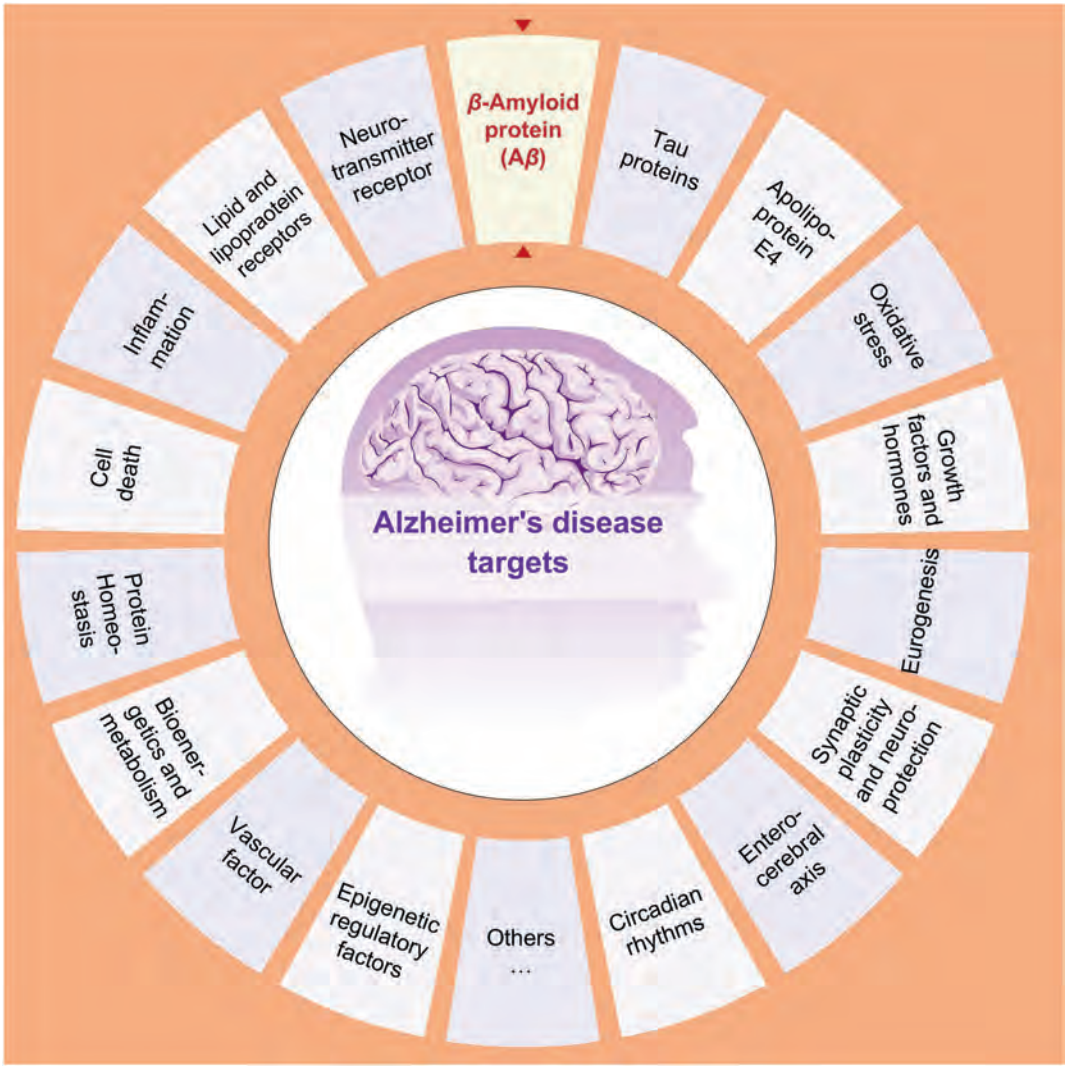

Figure 11 Common potential targets for Alzheimer's disease (AD). These include Aβ, tau protein, *APOE4*, lipids and lipoprotein receptors, neurotransmitter receptors, neurogenesis, inflammation, oxidative stress, cell death, protein homeostasis, bioenergy and metabolism, vascular factors, growth factors and hormones, synaptic plasticity and neuroprotection, gut−brain axis, circadian rhythm, epigenetic regulators, etc. Among them, the therapy targeting Aβ is dominant.

essentially nucleic acid molecules, which can be regarded as nucleotide analogs of antibodies, and can bind highly specifically to a variety of targets (from inorganic molecules, macromolecular protein complexes to the entire cell)[90]. At present, a variety of aptamers targeting AD-related molecular targets have been developed, such as aptamers with high affinity for β-secretase 1[91,92], and a number of DNA aptamers that specifically target Aβ_{40}[93]. This unique biomolecule combines the flexibility of small molecules and the high targeting of antibodies, and can achieve precise disease intervention that is difficult to achieve in traditional small-molecule drugs. In recent years, AI and ML technologies have been applied in the field of aptamer discovery and optimization. These technologies can significantly accelerate the design, screening, formulation optimization, delivery strategy development and customization of aptamers, and are expected to provide more efficient and accurate treatment options for complex diseases. For example, in 2021, a ML-guided particle display technology was reported to develop, validate, and improve experimental candidate aptamers, discover new aptamers and optimize their therapeutic properties[94]. Perez et al.[95] also developed an ML algorithm that can predict its binding ability based on the conserved primary and secondary structural characteristics of the aptamer (and considering parameters such as sequence abundance, stability, and structure). However, to date, no public research has been published to apply AI technology to the discovery of aptamers targeting Aβ, tau protein or other neurodegenerative disease-related proteins. Looking ahead, AI is expected to provide strong support for the formulation of personalized treatment plans by in-depth analysis of clinical, genetic and molecular data of AD patients.

3.2. *Drug design*

In the pharmaceutical industry, drug discovery and development are hampered by issues with traditional chemistry or chemical space, and the cost and time consumption of developing novel therapeutics is another obstacle in the drug design and development process. The development of a new drug typically costs

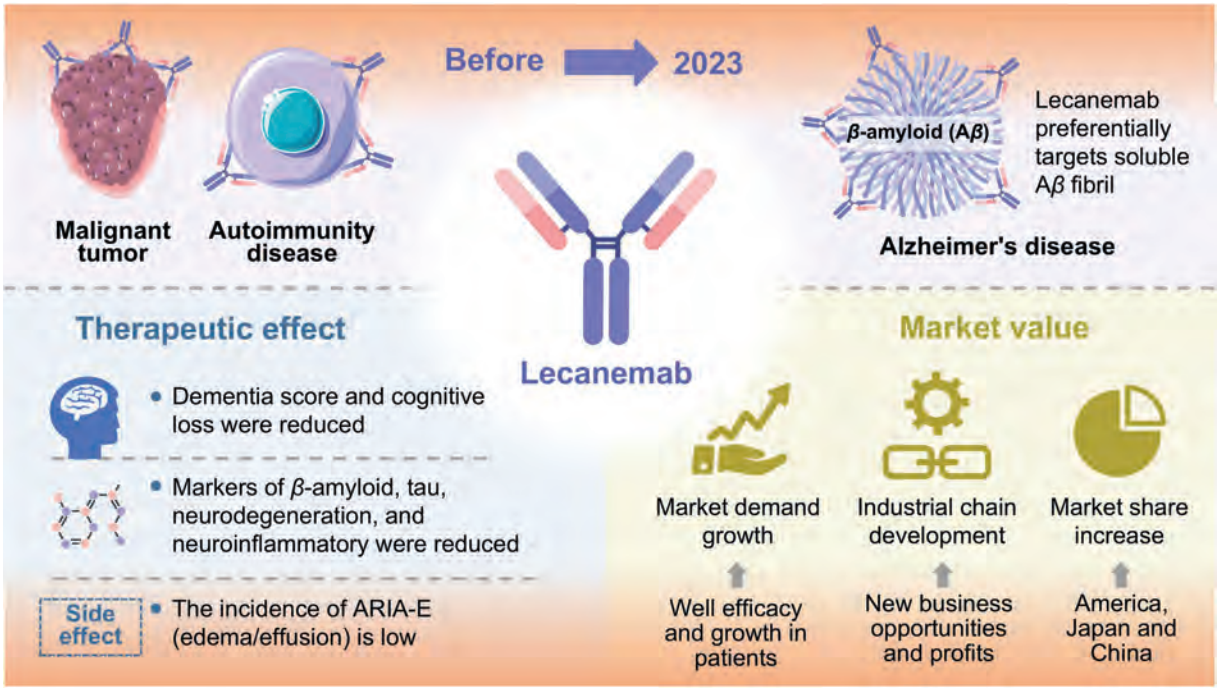

Figure 12 The initial design, application, therapeutic efficacy, and market value of Lecanemab in Alzheimer's disease (AD). Lecanemab was originally designed as a novel treatment for malignant tumors and autoimmune diseases. Due to its discovery of good targeting of soluble Aβ fibril, in 2023, Lecanemab became the first Aβ-targeted drug to be fully approved for the treatment of AD, and was confirmed in clinical trials as the first AD treatment to slow cognitive decline. At present, lecanemab has entered the medical system of the United States, Japan, and China, and has gained a certain market share. The market value potential is unlimited.

between $314 million and $2.8 billion and takes an average of 12 years[96,97]. How to reduce the cost of new drug research and speed up the development of new drugs has become a challenging and urgent problem that needs to be solved. As technology advances, computer-aided drug design integrating AI algorithms can eliminate the challenges and obstacles of traditional drug design and development. DL models, in particular, show great promise in drug design due to their powerful generalization and feature extraction capabilities.

3.2.1. De novo design

De novo design, that is, generating new molecular entities with desired pharmacological properties from scratch, is considered one of the most challenging computer-aided tasks in drug discovery because of the cardinal nature of the chemical space of drug-like molecules[98]. Estimates of potential drug-like compounds range from 10^{23} to 10^{60} [99]. DL has powerful learning and generation capabilities and has been used to automatically generate new structures with certain desired properties. Deep generative models learn the probability distribution of training data, extract representative features, produce low-dimensional continuous representations, and finally generate new data by sampling from the learned data distribution, including chemical fingerprints, simplified molecular input line entry system (SMILES), molecular diagrams, three-dimensional structures, etc[100]. Commonly used generative models such as recurrent neural networks, autoencoders, generative adversarial networks, and hybrid models. For example, Olivecrona et al. used the SMILES structures of molecules collected from the ChEMBL database to train a recurrent neural network to obtain SMILES strings. The recurrent neural network generated molecules with predicted biological activity by sampling the conditional probability distribution of the training set[101]. However, current de novo rely too much on text data such as SMILES and fail to deeply mine the rich structural information contained in molecular graphs, which is insufficient to meet the target-specific tasks in structure-based de novo drug design[102]. More critically, the current lack of a unified molecular interaction learning framework hinders people from learning from different data sets and refining key information. Integrating the 3D molecular geometry of the ligand and protein binding pocket into a DL-based generative architecture can solve part of the problem. For example, Google's DeepMind uses convolutional neural network to convert the amino acid sequence of a protein into a distance matrix and a torsion angle matrix and uses gradient optimization technology to convert these two matrices into the three-dimensional structure of the protein. AlphaFold was designed when used to treat a type of AD. Prediction of oligomer-selective vaccine immunogen candidates for disease showed almost the same results as the structure designed by Rosetta[103,104]. In order to strengthen information sharing between data and achieve unified molecular interaction learning, Fang et al. developed the first unified multimodal large language model molecular interaction learning framework—MolTC (Molecular inTeraction Modeling enhanced by Chain-of-thought theory). By using a multi-hierarchical chain-of-thought to optimize the thinking paradigm and training paradigm of large models, we can further collect and absorb a larger number and wider coverage of molecular interaction tasks, thereby more accurately grasping

the hidden molecular relationships[105]. At the same time, with its explicit and unified architecture, MolTC can still maintain accurate and efficient output in interactive tasks with few samples or even zero samples. Currently, the reliability of the MolTC framework has been verified among more than 4,000,000 molecules in multiple data sets, and its specific workflow can be seen Fig. 13[106].

3.2.2. *Drug screening*

According to the target and protein structure, screening suitable candidate compounds and identifying candidate molecules with potential medicinal effects are important steps in drug development. Drug screening is divided into high-throughput screening and virtual screening (VS). high-throughput sequencing technology is based on experimental methods at the molecular and cellular levels, uses microplates as experimental tool carriers, uses automated operating systems to execute the test process, uses sensitive and fast detection instruments to collect experimental result data, and uses computers to analyze experimental data[107-109]. VS is a technology that simulates the interaction between the target and candidate drugs, calculates the affinity between the two, filters out compounds that are unfavorable scaffolds in early drug development, and improves the efficiency of lead compound discovery[110,111]. The technologies used for VS are ML methods, pharmacophore-based methods, and similarity search methods[112]. In the field of AD, the development of potent acetylcholinesterase inhibitors has been an ongoing mission to treat AD-related dementia and improve the pharmacokinetic properties of existing drugs. David et al.[113] used a docking-based VS method to screen synthetic analogs of physostigmine and donepezil in the ZINC15 and MolPort databases and discovered 11 new acetylcholinesterase. Mendes et al. found three types of novel multipurpose compounds that simultaneously inhibit acetylcholinesterase, butyrylcholinesterase, and β-secretase 1[114]. Sang et al.[115] developed a novel butyryl cholinesterase inhibitor with good blood−brain barrier permeability and neuroprotective effects through extensive VS and pilot compound optimization determination.

In addition to focusing on the development of cholinesterase inhibitors, approaches targeting a broader aspect of AD pathology may have therapeutic potential. Intraneuronal inhibition disorders in AD and abnormalities in the exoneuronal microenvironment together lead to neuronal deterioration. Therefore, autophagy regulation strategies are more reliable for AD treatment. Li et al.[116] developed a multidimensional autophagy nanomodulator that enhances the autophagy degradation of neurotoxic aggregates and inflammasomes by activating the entire autophagy-lysosome pathway, thereby promoting Aβ phagocytosis. Emerging evidence emphasizes that mitochondrial autophagy damage mediates the accumulation of dysfunctional mitochondria in the AD brain[117]. Due to the scarcity of bioavailable neuronal mitochondrial autophagy inducers. Xie et al. developed a screening workflow combining AI and classic wet laboratory methods, using combined molecular representation methods, including Mol2vec, pharmacophore fingerprints, and 3D conformational isomer fingerprints for modeling, and two effective mitochondrial autophagy inducers (kaempferol and rhapontigenin) were obtained through iterative learning[118]. Both mitochondrial autophagy inducers increase the survival and function of glutamate and cholinergic neurons, eliminate Aβ and tau pathology, and improve animal memory. As AI develops and improves computing power, a further combination of AI with cross-species wet laboratory verification

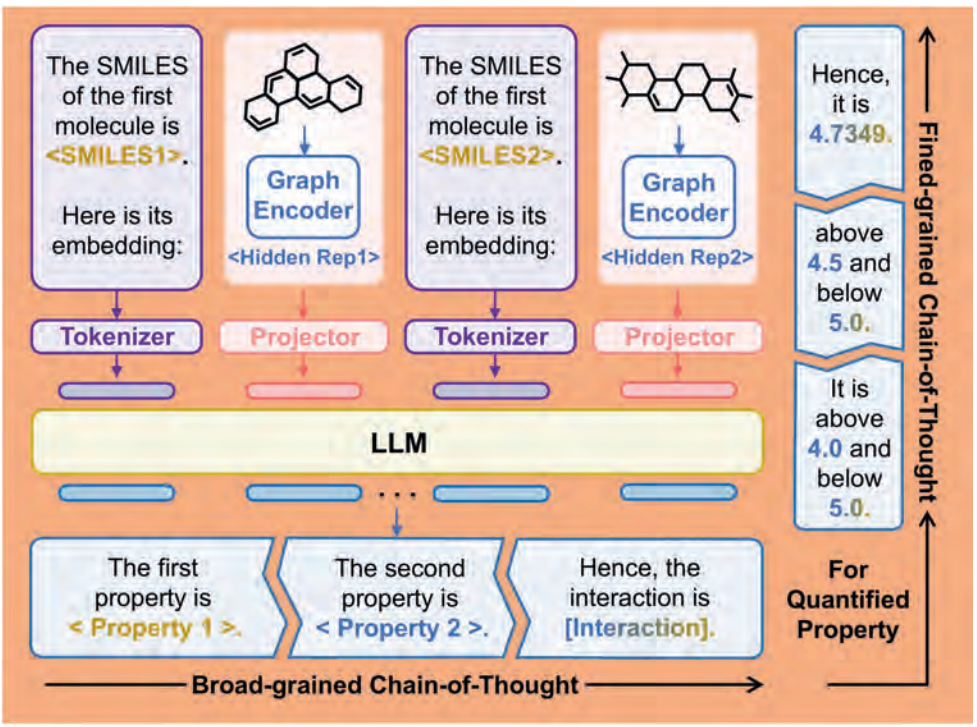

Figure 13 The framework of MolTC, a unified multi-modal framework for Molecular interaction modeling following the Chain-of-thought theory, which is enhanced by the principle of CoT. Reproduced with the permission of Ref. 106. Copyright © 2024 Association for Computational Linguistics.

will provide biological verification and help eliminate "false positive candidates". Ai et al.[119] successfully identified two powerful mitochondrial autophagy inducers obtained by Xie et al.[118] screening as described above by combining ML-based VS and cross-species-supported wet laboratory verification. This shows that the combination of AI and preclinical drug research can indeed improve the efficiency of pilot compound screening, reduce time and manpower consumption, and greatly accelerate the development of new AD therapies. A significant constraint in the advancement of AD therapeutics is the presence of the blood-brain barrier, which restricts drug permeability to the brain and diminishes drug efficacy. Recent advancements in AI-driven molecular screening have facilitated the development of innovative drug delivery systems, notably nanodrug carriers. Gong et al.[120] engineered a nanocomplex incorporating a proteolytic targeting chimera (PROTAC) specifically designed to target tau protein by splicing selected molecules. Nanomedicines exhibit high biocompatibility, low toxicity, and enhanced stability, offering renewed optimism for the treatment of AD and advancements within the pharmaceutical industry. Wei et al.[121] developed a nanomodulator that enhances blood−brain barrier penetration and targets microglia for the two-pronged regulation of chronically activated microglia-mediated neuroinflammation in AD. Xu et al.[122] proposed a nasal and brain delivery platform targeting lipid nanoparticles, providing a biocompatible, synergistic, and transformative therapeutic strategy for the multi-faceted management of AD.

3.2.3. Drug repurposing

Drug repurposing, also known as drug repositioning, refers to the identification of new uses for approved or investigational drugs beyond their original medical indications, perhaps in different dosages or different formulations[123]. The feasibility of drug repurposing lies in the fact that most drugs may have multiple targets, the targets may correspond to multiple effects, and the drug-disease relationship is highly diverse[112,124]. For example, sildenafil is a phosphodiesterase type 5 inhibitor that was originally developed to treat high blood pressure, but was later found to have significant benefits for erectile dysfunction and was approved by the FDA. It was later repurposed to treat a rare disease: pulmonary hypertension[125]. AstraZeneca's anti-cancer drug saracatinib is a dual-kinase inhibitor that was recently found to target Aβ in the brain and rescue synapse loss in mice[126]. Saracatinib has entered phase II clinical trials for AD drug development. Drug repurposing offers three advantages over developing an entirely new drug for a given indication. First, the risk of failure is lower if early-stage trials have been completed, demonstrating that the repurposed drug is safe enough in preclinical models and humans to be less likely to fail in subsequent efficacy trials. Second, drug development time can be shortened, with most preclinical testing, safety assessment, and formulation development already completed. Third, less investment is required, which can save preclinical and phase I and II costs[127]. Combining genome-wide association study, Xu et al.[128] proposed a DL framework based on network topology to identify disease-related genes, called NETTAG. They identified 156 AD risk genes rich in drug targets, combined network-based predictions with retrospective case-control observations of 10 million people, and found that ibuprofen, gemfibrozil, cholecalciferol, and ceftriaxone are associated with AD, associated with a reduced likelihood of disease. Similarly, Fang et al.[129] proposed an integrated network-based AI method that can quickly transform genome-wide association study findings and multi-omics data into genotype-based AD treatments, discovering that three drugs (pioglitazone, febuxostat, atenolol) were significantly associated with reduced risk of AD. Savva et al.[130] proposed a new network-based method for drug repurposing analysis in different AD stages (early, moderate, and severe). Clomiphene, camptothecin, and omacetaxine mepesuccinate were found to be suitable for early AD, paroxetine, gatifloxacin, and piperidolate for moderate AD, and tetrabenazine, iloperidone, and hydrocotarnine for severe AD. The above studies demonstrate that drug repurposing has become a fruitful approach to drug discovery. Specific studies on drug reuse can be seen in Table 3[76,128,131-137].

3.3. Drug prediction

It is well known that success rates in drug development are very low across all therapeutic areas and in the global pharmaceutical industry. Drug sensitivity prediction models can help improve clinical success, better understand a drug's mechanism of action, and identify the right drug for the right patient.

3.3.1. Predicting protein folding and three-dimensional structure

Protein structure prediction is generally based on the structural information of drug targets, analyzing and matching the protein structure, activation sites, and predicting interactions with other molecules. It is an important step in the drug discovery stage to guide the structure and properties of drug compounds[138]. Due to advances in genome sequencing technology, new protein sequences are growing at an alarming rate, with more than 200 million sequences currently in databases, but accurate de novo prediction of their three-dimensional structure remains an unsolved problem. Experimental protein structure determination methods include X-ray crystallography, nuclear magnetic resonance spectroscopy, and electron microscopy. These processes are tedious and will cost a lot of time and money, so it is necessary to develop algorithms for predicting the three-dimensional structure of proteins[112,139]. DL methods allow the extraction of complex features from protein sequence data and have been applied to predict protein secondary structure, backbone torsion angles, and residue contacts[140-142].

3.3.2. Predicting protein-protein interactions

Most biological processes, such as transcriptional regulation, signal transduction, and cell motility, are mediated by protein-protein interactions (PPIs), so analyzing PPIs is crucial for effective drug development and discovery[143]. The PPI interface is defined as a protein−protein binding site composed of multiple residues. It is a new type of drug target that is different from traditional drug targets such as G protein-coupled receptors, ion channels, kinases, and nuclear receptors[112]. PPI interfaces can form non-covalent interactions between side chain residues to promote multi-chain protein folding, and changes in local concentration, molecular collisions, and physicochemical composition may also alter interactions[144,145]. As part of the PPIs database, the String database contains approximately 1.4 billion PPIs obtained through experimental and bioinformatics methods[146]. Managing, analyzing, and modeling this data is a huge challenge in bioinformatics. Protein−protein interaction network (PPIN) based on DL methods can extract the most relevant sequence features to predict PPI interfaces, which can effectively solve the complexity of PPIs in biological systems. PPIN can simulate and

Table 3 The role of artificial intelligence (AI), computational biology (CB), and systems biology (SB) in new drug targets/drug reuse of Alzheimer's disease (AD). The contents in the table are quoted from ref [76,128,131-137].

Method	Drug	Mechanism/target/effect
AI in new drug targets/drug reuse of AD		
A network topology-based deep learning framework to identify disease-associated genes (NETTAG)	Ibudilast	Ibudilast targets (*e.g.*, PDE3A, PDE4B, and PDE4D) physically interact with proteins encoded by several predicted alzRGs (*e.g.*, BIN1, FYN, and GSK3B) inhibiting the production of pro-inflammatory cytokines and blocking neuroinflammation to prevent Aβ-induced cognitive impairment.
	Gemfibrozil	Gemfibrozil's targets (*e.g.*, LPL, PPARA, and SLCO1B1) have physical interactions with proteins encoded by several predicted alzRGs (*e.g.*, APOE, APP, HSPG2, and TOMM40), which reduced the amyloid plaque burden in a mouse model of AD.
	Ibuprofen	Ibuprofen targets interact with multiple protein products of predicted alzRGs (*e.g.*, MARK4 and FYN) to inhibit interleukin-1β (IL1B) protein levels and amyloid deposition in AD transgenic mouse models.
	Cholecalciferol	Targets of cholecalciferol, such as CDC25A, VDR, and GLRA1, physically interact with proteins encoded by several predicted alzRGs, such as GSK3B and MAPKAPK2. Vitamin D deficiency has been found to be associated with an elevated risk of AD.
	Ceftriaxone	The target of ceftriaxone interacts with multiple protein products of predicted alzRGs (*e.g.*, CSNK2A1 and TOP1) and was found to have neuroprotective effects by inhibiting amyloid deposition and neuroinflammation in mouse models of AD.
Bayesian ML model	Ruboxistaurin	Ruboxistaurin targets glycogen synthase kinase 3 beta (GSK3β) and inhibits tau phosphorylation.
Drug repurposing in AD (DRIAD) based on ML framework	Baricitinib	Baritinib inhibits JAK−STAT signal transduction pathway, inhibits inflammatory response and immune system activation. DRIAD prioritized baricitinib as a candidate AD drug, and baricitinib is being tested in an open-label, biomarker-driven basket trial in people with AD.
Multi-modal deep autoencoder in a network-based deep-learning approach (deepDR)	Isoproterenol	Isoproterenol is a non-selective beta-adrenergic receptor agonist that reduces amyloid plaques in patients with AD.
	Risperidone	Risperidone is an atypical antipsychotic that deepDR predicts may also have a potential impact on AD.
	Aripiprazole	Aripiprazole is an atypical antipsychotic predicted by deepDR to be associated with AD and supported by multiple evidence.
CB in new drug targets/drug reuse of AD		
High throughput screening	UMI-77	UMI-77 targets the MCL-1 receptor to induce mitochondrial autophagy to reduce ROS production and deposition of Aβ in damaged mitochondria.
High-throughput sequencing	Ketone body β-hydroxybutyrate (BHBA)	BHBA reduced Aβ accumulation and microglia overactivation in the brain; enhanced mitochondrial respiratory function of hippocampal neurons and protected them from Aβ toxicity.
SB in new drug targets/drug reuse of AD		
Proteomic analysis	Melatonin	Melatonin therapy reversed the abnormal expression of proteins in lysosomal signaling pathways, pathological phagocytosis of microglia, and mitochondrial energy metabolism; Improved mitochondria−lysosome fusion through Mcoln1, thereby improving mitochondrial function and alleviating Aβ pathology.
Network analysis based on gene list; protein-protein association networks	J147	J147 and its molecular target ATP synthase regulate stable mitochondrial Ca^{2+} levels and minimize SOCE activity to protect cells from a variety of acute neurotoxics.
Genome-wide association studies	PF-750	PF-750 is a drug that inhibits fatty acid amide hydrolase, targets the *EPHX2* gene, inhibits pathological accumulation of soluble epoxide hydrolase, and slows hippocampal atrophy in AD.

study complex cellular processes, such as signal transduction and protein complexes, thereby revealing the causes and potential treatments of various diseases, and can also be used to deduce the functional correlation of unknown protein interactions[147,148]. For example, Ceylan et al. analyzed transcriptome data from 403 patients by mapping data on the human PPIN, and discovered and analyzed patient-specific genes based on genes in the subnetwork, enriched functional terms, and known AD genes[149]. Tracy et al.[150] quantitatively compared the PPI of wild-type tau and frontotemporal dementia mutant tau in human neurons and found that the frontotemporal dementia mutation impaired bioenergetics and significantly reduced tau interactions with mitochondrial proteins.

3.3.3. Predicting drug properties

In drug design, an important consideration is the selection of drug candidates that possess a range of desired properties, particularly in terms of physical properties, biological activity, and toxicity. Physical properties, including solubility and permeability, significantly affect the bioavailability of pharmaceutical compounds and must therefore be integral considerations in the drug design process. Assessing biological activity is a crucial phase in the selection of efficacious drugs targeting specific biological entities. The examination of localized modifications in drug candidates and their subsequent effects on molecular properties and biological activity can be effectively conducted through the use of matched molecular pairs[151]. The integration of matched molecular pairs with DL methodologies has been employed to predict various bioactive properties, such as oral exposure, distribution coefficient, intrinsic clearance, and mode of action, etc[152,153].

Luo et al.[154] proposed DeepCpf1 based on a deep convolutional neural network, which reliably predicted the most effective and off-target effects of a given gene and identified key features of the guide RNA sequence, thereby determining the activity and specificity of genome editing. Tristan et al.[155] predicted new molecules with potential binding properties by encoding discrete chemicals into a continuous latent vector space and using graph convolutional networks to extract features of drug targets. Drug toxicity assessment is an important process in drug development. Predicting the toxicity of compounds can help guide the optimization of lead compounds and reduce the risk of failure during drug development. In recent years, DL models have achieved good results in toxicity prediction due to their ability to process a variety of chemical features and the advantages of automatically extracting features. For example, Mayr et al.[156] developed a multitask deep neural network model called DeepTox to predict toxicity. Jamal et al. combined biological, chemical, and phenotypic characteristics to analyze and predict drug-related neurological adverse reactions, and discovered the adverse reactions related to current AD drugs[157].

3.4. Pharmacokinetics

Pharmacokinetics mainly studies the changes in drug concentration in the body over time, involving ADME and other aspects, that is, the absorption (A), distribution (D), metabolism (M), and excretion (E) processes of drugs in the body[158]. With the improvement of computer speed and the implementation of quantum chemical methods, analyzing the kinetic properties of drugs can avoid a large number of repeated pharmacokinetic experimental processes. Liu et al.[159] developed Chemi-Net for ADME attribute prediction on 13 data sets, which is a fully data-driven DL method that does not require domain knowledge. The ADME prediction accuracy of Chemi-Net was found to be significantly improved, which will greatly accelerate drug discovery. ADME attribute prediction can be viewed as a classification or regression problem with strong feature representation capabilities, so we believe that the tight coupling of graph convolution ADME predictors and medicinal chemistry collaboration will improve the speed and reliability of drug development.

3.5. Clinical trials

When a drug candidate successfully passes all preclinical testing, it is used in clinical trials to determine the efficacy and safety of the investigational drug. Clinical trials have high failure rates, which not only undermines investment in the trials themselves but also preclinical development costs. Each failed clinical trial costs $800 million to $1.4 billion[160]. Suboptimal patient cohort selection and recruitment techniques, coupled with the inability to effectively monitor patients during the trial, were the main reasons for the high trial failure rate. In March 2024, Japan's Kobayashi Pharmaceutical Company's health products containing red yeast rice showed symptoms such as kidney disease. It may be that there were problems in the safety evaluation during the clinical trial phase, resulting in health risks and high recall costs. AI can help overcome these shortcomings of current clinical trial designs: DL can automatically find patterns of meaning in large data sets such as text, speech, or images, natural language processing can understand and correlate content in written or spoken language, and human-machine interfaces allow information to be exchanged between computers and humans[160]. CB and SB can correlate large and diverse data sets, such as electronic health records, medical literature, and trial databases, to match patient recruitment to trials before they begin, by analyzing toxicities, side effects, and other relevant parameters to improve the success rate of clinical trials and thereby reduce the cost of clinical trials[161]. For example, IBM Watson developed a clinical trial matching system that can create detailed clinical profiles using patients' medical records and clinical trial data[162]. To sum up, we believe that AI, CB, and SB will provide better help for clinical trials.

4. Role in Alzheimer's disease adjuvant treatment

In the past few decades of AD drug development, except for cholinesterase inhibitors and memantine, which can relieve or stabilize symptoms for a limited period of time, there is currently no drug that can prevent the progression of AD. Adjuvant therapy is considered a new opportunity for AD treatment.

4.1. Photobioregulation

Photobiomodulation (PBM) is the use of specific red to near-infrared wavelengths to regulate brain function as a promising therapy that can address the complex pathophysiology of AD in a single intervention. In recent years, photobiological regulation of 600−1070 nm near-infrared light has rapidly developed to treat AD and traumatic brain injury[163]. Previous studies have shown that PBM not only prevents early memory decline but also rescues late memory defects in *Samp8* mice[54]. Further research has found that PBM can reduce the size and number of Aβ plaques in App/Ps1 mice and improve cognitive function in patients with dementia. After 2 months of PBM treatment, the neuron morphology of AD mice returned to a normal spindle shape. At the same time, after 6-month-old AD mice were irradiated with PBM, the size of the senile plaques also significantly decreased, and the number of neurons around the senile plaques was also significantly increased[53,54]. PBM illumination also directly reduced Aβ-mediated extracellular space obstruction and restored the flow of interstitial fluid; it enhanced FDH activity and attenuated FA-mediated Aβ toxicity. Equally important, PBM inhibits phosphorylated tau-related molecular pathways, increases microtubule-associated protein immunoreactivity, and reduces glial fibrillary acidic protein-positive reactive astrocytes and CD45-positive reactive microglia[53], see Fig. 14[50].

For further verification, Yue et al.[53] used molecular simulations and found that PBM illumination reduced the formation of SS

bonds between CYS97 and CYS100 induced by Aβ_{42} and partially restored the formation of SS bonds between CYS103 and CYS111 in ADH5, see Fig. 8. This shows that 630 nm Red light can reverse inactivated ADH5. PBM has low phototoxicity and high tissue penetration, and can non-invasively reverse aging-related cognitive decline. This discovery provides a promising opportunity to translate PBM into a clinical treatment for patients with dementia.

In addition, studies have shown that the combination of light therapy and nano-Q10 may be more effective in treating AD than either method alone. Serum coenzyme Q10 (CoQ10) has a protective effect in neurodegenerative diseases and is helpful in the treatment of AD. After nano-packaging, nano-CoQ10 with a diameter of 30 nm can penetrate the blood−brain barrier, follow the interstitial fluid flow into the deep cortex, and reduce intracellular Aβ oligomers and extracellular senile plaques[48]. Therefore, combining these two methods to accelerate interstitial fluid drainage will facilitate drug delivery and restoration of nerve signals, see Fig. 14. However, red light has thermal effects, and near-infrared or red light over 650 nm has been found to cause strong side effects such as irritability, headache, eye fatigue, sleep disorders, and insomnia[164]. Therefore, optimizing certain generalized parameters of PBM may bring benefits to AD patients, including parameters such as wavelength, power density, dose, light source positioning, and pulse frequency. AI based on ML and neuronal networks is rapidly becoming a realistic prospect in the PBM field. AI can optimize PBM in a variety of ways. For example, AI algorithms can be developed to analyze patient data to provide personalized treatments, including optimal treatment wavelength and exposure duration, by evaluating disease severity scores and monitoring patient responses to PBM in real time. Shi et al. used a fast label-free identification method based on AI-assisted terahertz imaging to identify the therapeutic effects of different light wavelengths and irradiation times[165]. Phan et al.[166] proposed a real-time closed-loop system for monitoring and controlling the temperature of phototherapy, using a contactless infrared thermal sensor array and an artificial neural network to induce thermal damage in predetermined areas on tissues. These controllers are implemented on an embedded platform (Jetson Nano) for real-time thermal control. Kim et al.[167] introduced a low-power wireless telemetry technology based on DeepLabCut (DLC), and established a series of guides through the optimization combination of analog generation wavelength and light source. López-Marín et al.[168] used state-of-the-art computing techniques and simple models to understand the impact of PBM on long-term scales. In short, PBM represents a multifaceted therapeutic intervention in AD, with great potential that can be achieved by optimizing parameters. Future research should optimize these parameters by combining AI, CB, and SB.

4.2. *Brain stimulation*

Noninvasive brain stimulation technology has attracted great interest in AD research, providing opportunities to directly interact with brain functions in a non-invasive, safe, and painless way, with good temporal resolution and relatively high spatial accuracy, which can help early disease detection and improve cognitive function. Two of the most commonly used transcranial methods namely transcranial magnetic stimulation (TMS) and low-intensity transcranial electrical stimulation (tES).

The TMS method has been successfully used to study molecular and neurotransmitter dysfunction characterizing AD pathology and to differentially diagnose AD and other forms of dementia[169-171]. Lin et al.'s study[172] showed that TMS treatment effectively delayed the decline in long-term memory of new objects and locations in 5 × FAD mice, and significantly improved the drainage efficiency of brain clearance pathways, including the lymphatic system and meningeal lymphatic vessels in the brain parenchyma[172]. Significant reduction of Aβ deposits, inhibition of microglia and astrocyte activation, and elevated c-FOS expression were observed in the prefrontal cortex and hippocampus of TMS-treated 5 × FAD mice[172]. In addition, TMS improves individual cognitive abilities by targeting various brain regions and functions. The clinical study by Koch et al.[173] showed that the clinical dementia rating scale in patients receiving precuneus TMS has better performance, indicating that TMS targeting precuneus lobes can slow down cognitive and functional decline in patients with AD. However, because the complex anatomy of the brain seriously affects the shape and strength of the electric field sensed by the TMS coil, it is difficult to accurately locate specific brain regions. Yokota et al. used deep neural networks and volume conductor models to determine the relationship between MRI images and electric fields, thereby constructing a specific brain anatomical model[174]. Dougherty et al.[175] proposed a mathematical multi-scale model that demonstrates the validity and medical applicability of the model by using idealized computational simulations of two-dimensional domains, and then uses MRI-derived three-dimensional human head geometry with inhomogeneous and anisotropic tissue conductivity. Reijonen et al.[176] developed a pipeline that fits brain maps to a single brain, enabling visualization of target areas during TMS sessions. Furthermore, the position and orientation of the TMS coil significantly affect the evaluation and regulation of cortical excitability. Therefore, Rashed et al. estimate personalized conductivity values through anatomical information obtained from T1 and T2-weighted MRI scans through convolutional neural networks, providing the brain electric field distribution[177]. Zhong et al.[178] used the CASIA dataset to construct a stimulus effect map framework to determine the optimal coil placement without the need for TMS electric field simulation segmentation or meshing, making TMS evaluation and treatment easier and more accurate.

On the other hand, tES utilizes surface electrodes of different polarities (anode or cathode) to transmit current through the intact scalp, thereby regulating the polarization of neurons or axonal membranes. Benussi et al.[179] found that applying γ-frequency transcranial alternating current stimulation in the prefrontal cortex can safely and effectively induce the entrainment of nerve oscillations in AD patients, improve memory function, and improve cholinergic defects. However, the potential complexity of nonlinear responses to electrical stimulation makes it challenging to design precise and effective neural regulatory schemes. Therefore, computational models become indispensable in understanding and controlling neural responses to electrical stimuli. ML models can predict and identify the presence of disease symptoms based on neural activity and adaptively learn to regulate stimuli, becoming a key tool in developing a closed-loop system for brain stimulation. For example, Boutet et al.[180] constructed an ML model that predicts the optimal settings for brain stimulation using fMRI results, thereby optimizing the clinical benefits generated by brain stimulation. By leveraging advances in high-performance computing and parallel programming, Hussain et al.[181] proposed an ML framework, AxonML, to evaluate and optimize the response of nerve fibers to electrical stimuli, including unipolar and multipolar stimuli, fiber diameter, neuromorphism, stimulation waveform, intrinsic neural activity status,

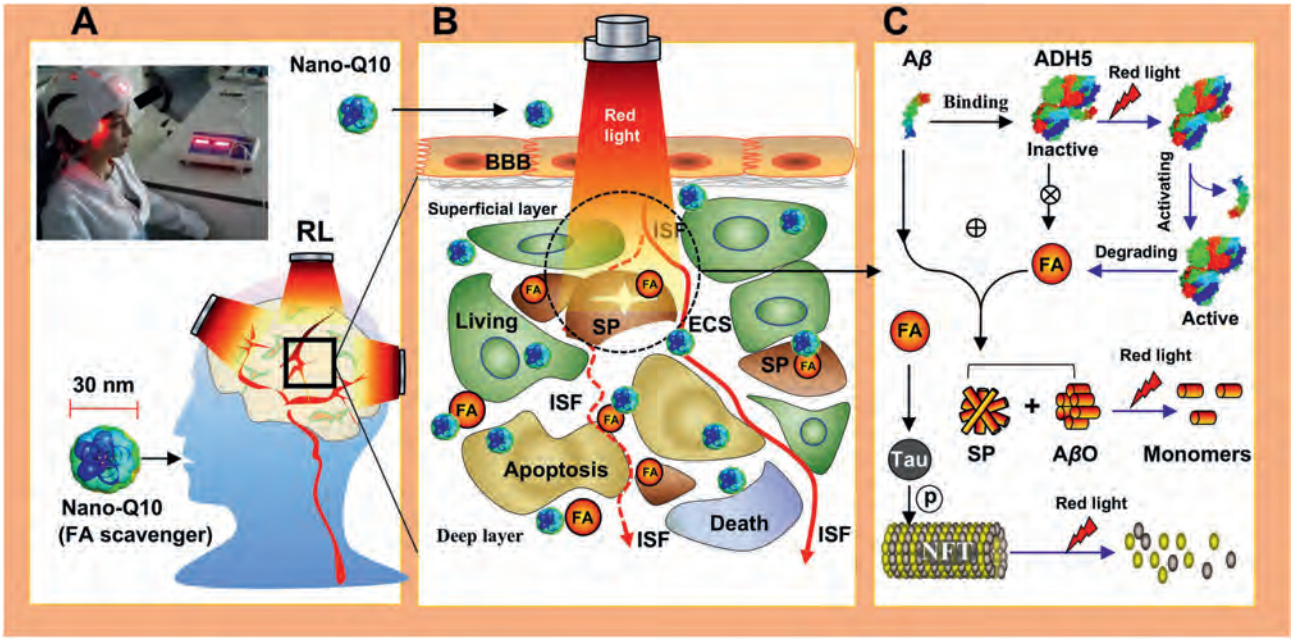

Figure 14 Model of a new therapeutic strategy for treating Alzheimer's disease (AD) combining red light with nano-packed Q10. (A) Combination therapy of red light (RL) and Nano-Q10. (B) RL-destroyed senile plaque (SP) in AD. (C) The effects of RL on SP and neurofibrillary tangles (NFTs). Reproduced with the permission of Ref. 50. Copyright © 2024 International Journal of Biological Macromolecules.

and neuroregulatory schemes. Sun et al.[182] proposed a pedal hill modeling to establish an optimal excitation model with maximum torque efficiency optimization objectives. A new model based on the particle swarm optimization algorithm, the backpropagation neural network algorithm, and the proportional integral derivative control composite algorithm is also proposed to determine effective stimulation modes. Therefore, the model built on ML helps to improve the personalization of detection and stimulation.

4.3. Cognitive training

Cognitive training (CT) is a treatment that focuses on guided practice of specific cognitive function tasks. A large amount of evidence shows that CT can improve cognitive functions in AD and MCI, which may be because the cognitive mental activities stimulated by CT enhance the functional network connectivity and functional efficiency of brain regions and regulate brain plasticity[183-186]. With the advancement of computer software and hardware technology, in the field of CT, computer technology-based interventions have produced generally superior results in enhancing cognitive function and quality of life compared with traditional CT. Computerized cognitive training (CCT) involves guided drills and practice on standardized tasks designed to load specific cognitive processes, often without explicit teaching of memory or problem-solving strategies. CCT can target single or multiple domains and typically adjusts task difficulty based on individual performance[185]. The most commonly used applications for CCT include Brainer, CogniFit, and Cogmed. Studies have shown that in patients with MCI, CCT is effective on global cognition, memory, working memory, and attention, and helps improve psychosocial functioning, including depressive symptoms[185].

In addition to CCT, VR-based cognitive training has also been actively researched. VR refers to an environment or situation created by artificial intelligence technology using computers, which can provide an immersive space and time experience. VR environments can also tailor assessments and interventions to the needs of the subject. Son et al. have shown that VR-based cognitive training is beneficial in improving the activities of daily living and instrumental activities of daily living in patients with MCI and AD[187]. However, different cognitive impairments exhibit different characteristics and may respond differently to CT interventions. Wide variation in intervention protocols, such as type, duration, intensity, and frequency of CT, may also lead to inconsistent results[188]. Hence, when designing CT applications, it is important to match the technology to older adults' needs and evaluate their experience. The improvement of overall cognition and daily functioning of AD patients after memory support and healthy lifestyle training can be collected with the help of the Electronic Memory and Management Assistance digital application, to develop more acceptable, adaptive, and scalable compensatory and lifestyle interventions, providing information[189].

5. Challenges for AD conversion

Advances in ML algorithms, especially DL methods, as well as improvements in architectural hardware and the ease of access to big data, herald great potential for the application of AI, CB, and SB in AD. But there are also some challenges and potential pitfalls, including privacy protection issues, data availability, model interpretability, ethical issues, etc.[190].

In terms of privacy, some biological data, especially human genomics data and commercially sensitive pharmaceutical data, often involves a large number of privacy issues, and computers must be responsible for this data when conducting research. Although a variety of data encryption and anonymization technologies currently exist to ensure that patient privacy is not leaked, there are still many challenges in privacy protection. On the one hand, the privacy protection measures of DL models when

integrating multi-party data are not yet perfect; on the other hand, the privacy protection regulations for medical data are not yet unified at this stage, and the laws and regulations on the protection of medical data privacy vary greatly in different countries and regions. Based on this, researchers urgently need to develop new privacy protection algorithms and frameworks to maximize data security and privacy during the training and application of DL models. For example, blockchain is a new type of database software that uses distributed networks, encryption technology, smart contracts, and other technologies to achieve data sharing, verification, storage, and transactions. It can ensure the transparency and immutability of the data processing process, thereby ensuring the to a certain extent, it alleviates the trust problem between patients and researchers[191].

On the data side, a key issue is the performance of the model. A large number of parameters need to be optimized in DL, resulting in a high risk of overfitting. The reported performance is likely not to reflect the true ability of the model to classify/predict/segmentate. And in the population, the number of AD patients is far less than that of healthy people, and there is a class imbalance problem, which will lead to further decline in performance. Another data-related problem faced in AD research is high dimensionality. AD is a highly heterogeneous disease. When making early predictions, diagnoses, and developing corresponding drugs for patients with AD, it is necessary to fully consider the heterogeneity of AD and conduct a multi-dimensional comprehensive analysis.

On the model side, DL's complex series of matrix multiplications and abstract filters create a "black box" problem for models: that is, the algorithm can inform clinicians or researchers of its predictions, but cannot provide further information as to why it made the predictions it did[192]. Furthermore, the ever-increasing number of models leaves non-experts helpless as they cannot decide which model to choose to solve their problems. As such, explainable AI is working to increase the transparency of algorithms, producing models that more easily explain their findings, thus increasing human trust and understanding of their predictions.

In terms of ethical issues, the challenges of DL mainly involve the principle of not harming and benefiting the patient, and fully respecting the patient's autonomy and informed consent[193]. DL models can uncover personal genetic risks in AD diagnosis, affecting patient privacy and potentially impacting their mental health and social life. Due to cognitive impairments, AD patients may struggle to grasp the research purposes and risks. Thus, researchers must ensure that patients or their legal representatives are fully informed and provide informed consent.

6. Outlook

AD is a syndrome characterized by functional and cognitive decline. Regarding the pathogenesis, various hypotheses have been proposed, but none of them can explain the full picture. With more public databases and improved computing power, new technologies now allow for large-scale analysis of complex biological processes and diseases. For complex diseases like AD, analyzing only one or a few dimensions is insufficient to understand their causes. Thus, sophisticated methods are needed to integrate multiple data types and identify disease-specific factors.

AI methods for AD research have shown promising results, providing insights into the diagnosis and treatment of AD due to their ability to process large amounts of clinical, biological, environmental, and lifestyle data. For example, neuroimaging data analyzed by DL algorithms can reveal subtle changes in brain structure and function, thereby providing a basis for early diagnosis of AD. In the study of AD heterogeneity, SB can explore the molecular interactions and network regulation in disease states by integrating multi-source heterogeneous data, such as genome, transcriptome, proteome, and metabolome data, and provide fresh insights into the complex pathological process of AD.

In AD drug development, CB can utilize extensive drug data to design new drugs, identify targets, optimize properties, study pharmacokinetics, and conduct clinical trials. Future AD research will benefit significantly from innovative interdisciplinary methods to enhance understanding of disease mechanisms and treatment strategies. Although AI, CB, and SB translational research in AD is still emerging, we believe that improvements in data quality, sharing, and analysis, along with advances in SB analysis and computing power, will lead to an integrated framework. This will greatly enhance our understanding of AD pathogenesis and aid in creating new intervention strategies.

This article primarily examines the roles and current challenges associated with AI, CB, and SB in the context of translational research on AD. The robust data processing capabilities and computational models inherent in ML offer novel avenues for exploring mechanisms, diagnosing, and treating AD. Nevertheless, this technology presently encounters significant challenges related to privacy protection, data availability, model interpretability, and ethical considerations, necessitating ongoing optimization and enhancement in future applications.

Declaration of generative AI in scientific writing

Artificial intelligence (AI) and AI-assisted technologies were not used in writing this manuscript.

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Author contributions

Shulan Jiang and Zixi Tian wrote the manuscript. Yuchen Yang, Xiang Li, Feiyan Zhou, Jianhua Cheng, Jihui Lyu, and Tingting Gao were responsible for the conception and design of the review. Ping Zhang, Hongbin Han and Zhiqian Tong supervised and revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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