Network Biology Approaches in Alzheimer's Disease

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Alzheimer's disease (AD) is a polygenic multifactorial neurodegenerative disease that is without a cure. There are some symptomatic treatments to manage the psychological symptoms but none of these drugs can halt disease progression. Additionally, many anti-AD drugs failed in late stages of clinical trials and many hypotheses surfaced to explain these failures, including the lack of clear understanding of disease pathways and processes. Different epigenetic factors have been implicated in AD pathogenesis; thus, they could serve as promising AD diagnostic biomarkers. Additionally, network biology approaches have been suggested as effective tools to study AD on the systems level and discover multi-target-directed ligands as novel treatments for AD.

Alzheimer's disease (AD) diagnostic biomarkers drug prioritization network biology neuroscience

1. Introduction

Alzheimer's disease (AD) is a polygenic and multifactorial disease characterized by the deposition of amyloid-β (Aβ) fibrils in the brain, leading to the formation of plaques and neurofibrillary tangles (NFTs), and ultimately resulting in dendritic dysfunction, neuronal cell death, memory loss, behavioral changes, and organ shutdown [1][2][3][4][5]. It is estimated that 6.5 million Americans, 65 years and older, are living with Alzheimer's dementia, and this number is likely to grow rapidly [6], reaching 13.8 million by 2060 [6][7]. Additionally, approximately 10 million Americans are currently living with mild cognitive impairment (MCI). In fact, 50% of MCI cases are due to AD based on biomarker evidence [8]. Eventually, 15% of MCI patients develop dementia after two years, and one-third develop dementia due to AD within five years [6]. The number of Americans with AD-MCI and AD dementia is approximately 11.2 million [6]. The healthcare cost for AD patients in 2022 is expected to reach USD 321 billion [6]. Furthermore, as the global population ages, the number of people suffering from dementia is expected to triple from 50 million to 152 million by 2050 [9]. Therefore, there is an urgent need to impede or slow down the onset and progress of the disease and ameliorate the disease-debilitating symptoms in hopes of putting an end to this disease and preventing a growing public health crisis [10].

Multifactorial mechanisms are involved in AD pathogenesis, including genetic, epigenetic, biological, and environmental factors networking with each other [11]. However, genomic experiments affirmed that no particular gene could be assigned as a potential target for AD pathogenesis. In fact, multiple genetic and non-genetic factors contribute to disease development [11][12][13][14][15][16][17][18]. In the past decade, there has been an increased

understanding of potential targets for disease-modifying therapies that delayed or slowed down the clinical course of AD. According to the U.S. National Library of Medicine's (NLM) ClinicalTrials.gov Beta (beta.clinicaltrials.gov) [19], there have been 1943 clinical trials of different phases and different designs to investigate new potential molecules in treating AD. Among these studies, 151 clinical trials progressed to Phase III clinical trials, in which safety and monitoring of side effects were investigated.

After decades of AD drug discovery research and billions of dollars spent on clinical trials, researchers still do not have a single effective anti-AD drug. Promising novel strategies to developing anti-AD drugs keep failing in clinical trials [20][21]. The exact cause of the disease remains the subject of ongoing debate and investigation. At this time, the most plausible hypothesis is that AD is a multifactorial disorder in which genetic and environmental risk factors interact, leading to an acceleration in the rate of normal aging. More than 600 genes contribute to AD pathogenesis, along with environmental factors and epigenetic changes [4][5]. The genetic deficiencies in AD consist of germline mutations, mitochondrial DNA mutations, and single-DNA nucleotide polymorphisms [22][23].

Therapeutic clinical treatment targets of AD aim to enhance behavioral, cognitive, and non-cognitive symptoms of the diseases. In the last two decades, there were no new medication approvals for the treatment or the prevention of AD. Currently, the aim of developing new anti-AD agents is to utilize new disease-modifying agents that delay the onset or slow down the progression of an established disease. Aβ, tau protein, and cell oxidation are the most currently promising targets to modify the pathologic status of Alzheimer's disease [24].

2. Exploiting Network Biology Approaches in Alzheimer's Disease Research

Network biology approaches have been suggested as paradigm-changing approaches for the discovery of disease biomarkers, drug targets, and effective drugs for polygenic multifactorial diseases, including cancer, diabetes, psychological disorders, and AD. However, the typical focus on one single type of omics has been a limiting factor for the success of previous systems biology studies because the findings were explaining only a modest portion of the complex disease, and AD was no exception. Therefore, future studies should study multiple omics data simultaneously and apply new technologies, including machine leaning (ML) and artificial intelligence (AI) to derive novel multi-system and multi-target hypotheses.

2.1. Previous Alzheimer's Disease Drug Discovery Failures

Misunderstanding of the disease mechanisms coupled with inconsistent drug development protocols that relied on single-target approaches, in addition to the improper management of drug discovery projects, led to the inopportune nomination of drug targets which contributed to many drug failures [3][25]. Additionally, clinical trial design utilized in drug discovery failed due to many reasons, including the delay in initiation of treatments, incorrect drug doses, or lack of good drug-monitoring biomarkers [26][27]. The success rate in progressing AD clinical trials from one phase to the next has been poor, and the number of therapeutic agents approaching FDA approval is low [28]. Failures in clinical trials might be due to ineffective treatments, drug side effects, or misconducted trials [28].

The improper selection of methodological parameters in clinical trial design [29] impeded the success of previous clinical trials [26][27][28][30]. In fact, the clinical trials dilemma in psychiatry, neurology, and AD has been discussed elsewhere by many researchers [31][32][33]. Issues including inaccuracy, incorrectness, and bias hindered clinical trials success [34][35]. Other factors included personal errors, drawbacks in rating scales, and limitations in neuropsychological tests leading to errors regarding the underestimation of the clinical outcome in clinical trials [29][36]. Increasing the number of clinical trials investigating drug effects has been associated with better treatment outcome [28].

Additionally, limitations in cell-based models to probe neurodegenerative diseases, such as AD, contributes to AD failure treatment [37]. The complexity of CNS motivates researchers to integrate the molecular basis of neurodegenerative diseases with the unique organization and construction of brain tissue [37]. This combined approach is displayed via 3D cell models accompanied by microfluidic technology, which are in their early stages and ready for improvement [37]. Subsequently, this integrative system should enrich the preclinical drug development pipeline [37]. The biodiversity of AD-drug design and development needs to unify healthcare workers' and scientists' efforts [28]. Other factors that played an important part in the failure of many AD drug development programs were improper diagnostic evaluations, elusive genetic factors, and/or concomitant diseases [38][39].

2.2. Network Biology Approaches Hold the Promise to Revolutionize Alzhiemer's Disease Research

AD is a complex disease associated with multiple perturbations in biological networks and functional network connectivity that are fundamental for normal physiological function; hence, multi-target treatment approaches seem imperative to treat the disease [40][41][42]. Studies have reported that numerous brain functional networks are significantly impaired in AD patients, including the control network (CON), default mode network (DMN), dorsal attention network (DAN), salience network (SAL), and sensory–motor network (SMN) [43]. In mild AD patients, there is evidence indicating reduced functional network connectivity in the brain is a predisposing factor. Additionally, the DMN is impaired in very mild to mild AD patients, while severe AD patients suffer from disrupted network crosstalk [43]. Thus, network and systems biology approaches that target multiple disease networks and pathways hold great promise to revolutionize AD drug discovery research.

Furthermore, network biology approaches enable the identification of novel disease biomarkers, including quantitative diagnostic and prognostic biomarkers, imaging, and biochemical tests. Novel validated disease biomarkers could potentially equip AD researchers with the proper tools to accurately differentiate between AD and non-AD dementias, which can positively impact drug discovery efforts, clinical trial design, and patient selection for clinical trials [44]. There is agreement among scientists [1][2][3][4][5][22][45] that future AD research should focus on the following: (1) reassessing previous and current prevalent AD pathogenesis hypotheses, (2) identifying effective disease-specific biomarkers, (3) re-evaluating previous disease diagnostic standards, (4) considering new guidelines and procedures for disease control, (5) reorienting drug discovery efforts toward employing approved multi-target approaches and pharmacogenetic hypotheses, (6) updating the managerial requirements for drug

design and development, (7) applying pharmacogenomics approaches in biomarker and drug discovery and development, and (8) implementing disease-prevention strategies for susceptible individuals.

2.3. Current Network Biology Efforts

The underlying hypothesis of network medicine has been recruited in the development of multi-target ligands and combination drugs [21]. The multi-target ligands and combination drugs are considered promising network medicines for challenging and complex diseases [46][47]. Clinical studies showed that multi-target ligands and combined drugs are more effective than single-target drugs in complex diseases treatment, including depression, cancer, and infectious diseases, such as the acquired immunodeficiency syndrome (AIDS) [48][49][50][51]. Combining donepezil and memantine improve the brain's cognition function, and patient's overall status in mild and advanced AD. Additionally, such drugs decrease the rate of clinical decay and are safe and tolerable [46].

The idea of network medicine is based on the hypothesis that diseases occur due to the disruption of biological networks responsible for homeostasis as a result of activation or deactivation of certain proteins or biochemical reactions, which eventually disturb the balance of normal physiology pathways [52][53][54]. Hence, disease networks are complex disease processes that are caused by irregular diverse genes, proteins, and signaling cascades [47]. Therefore, network medicines intend to restore disrupted disease networks to their default normal physiology status by targeting multiple key effectors in disease pathways [47].

Recent advances in multi-omics data analysis coupled with advancements in computational chemical biology methods led to better disease understanding. As a result, network medicines have been suggested as potential surrogates for identifying effective treatments for complex diseases, including AD [40][41][42][55]. Additionally, the application of network approaches to AD research projects has shed light on a crosstalk among diverse signaling pathways involved in AD pathogenesis [21]. Further work is required to lay the groundwork for the development of the next-generation anti-AD drugs. Furthermore, the diverse disease networks could not be revived through targeting of a single protein and/or signaling cascade because there are numerous active and spare cellular mechanisms in biological systems [56].

2.4. Multi-Target-Directed Ligands as Network Biology Treatments

The Multi-Target-Directed Ligands (MTDLs) approach is one of the most promising therapeutic interventions for AD patients as well as other complex multifactorial diseases, including cancer, diabetes, and other psychological disorders [57][58][59]. The design of MTDL hypothesizes that successful disease-modifying treatments of AD should target systems biology pathways rather than selectively targeting individual proteins or drug targets [60][61]. As such, MTDLs can be defined as drugs and/or technologies designed to interact with more than one target involved in the pathogenesis of a defined disease [61][62][63][64][65][66][67], surpassing the "one-molecule, one-target" model [52][58]. It has been theorized that potent MTDL should simultaneously target the typical signs of AD, such as the irregular accumulation of Aβ peptides [68][69][70][71][72], tauopathies [73][74][75][76], and the cholinergic insufficiency in CNS [77][78][79]. In addition, the effective MTDL should consider other AD features, such as the oxidative and nitrosative

stresses [80][81][82], inflammatory response of brain and spinal cord, excitotoxicity [83], mitochondrial dysfunction [66][84][85], aberrances in calcium [86][87] and other metals [19][88][89], and irregularities in apolipoproteins [90][91].

It is suggested that the rational design of MTDLs can be achieved by two approaches: (1) drug repurposing, considering drug design methods that take into account the biological fingerprints (or biological spectra) of familiar active drugs against other therapeutic receptors where one or more drugs can modulate several targets [92][93][94][95][96] and (2) fragment-based drug design, which is based on the core structures of active compounds against specific targets to generate a new merged scaffold with dual or multiple activity against two or more targets [92].

In the first approach, compounds are screened against multiple proteins/drug targets to retrieve hits with the desired biological profiles [93][94][95]. The main advantage of this approach is that the investigated compounds are often commercially available and clinically proven to be safe, thus reducing development time and costs [92][93][94], and most importantly, the proposed lead might act as a synergistic effector, modulating the disease pathway effectively [97]. However, the optimization protocol of the biological activity of the lead compound to fit the new disease application has been limited [92][93][94]. Therefore, more work is required to improve hit identification and lead optimization. Sometimes the pharmacokinetics properties of the lead hinder the application to new diseases such as AD where drugs have to meet the criteria for CNS drug design [98][99]. The latter, fragment-based, MTDL approach can be designed using three main methods: (1) linking active fragments/compounds using a linker/spacer and keeping known pharmacophoric features [92], (2) fusing or integrating the active compounds to generate a new chemical entity that shares identical features [92], and (3) merging/mixing the selected bioactive compounds to yield a scaffold that has the key functionalities of the pharmacophore [92].

Studies indicated that the major impedance of the MTDL success is the need to maintain or boost the biological activity of the prioritized compounds while preserving drug-like properties [100]. Many MTDLs may have limitations due to lower selectivity towards some drug targets [101][102][103][104][105][106], while drug development efforts focusing on increasing the biological activity of MTDL may increase the risk of drug toxicity [101][102][103][104][105][106]. Therefore, MTDLs should be optimized by improving the selectivity towards certain protein targets while reducing drug toxicity [103][104][105][106]. Additionally, the designed chimeric entities using the fragment approach have higher molecular weights than the parent compounds, which may affect drug-like properties, while at other times, the merging protocol might be a promising solution for developing oral bioavailable drugs [107][108][109].

Finally, when considering MTDL, it is crucial to pay special attention to the required physicochemical properties, including pharmacokinetics, pharmacodynamics, hydrophilicity, and hydrophobicity [92]. MTDL design against neurodegenerative disorders should take into account the drug's blood–brain barrier permeability [98][99].

2.5. Suggested Disease Biomarkers and Disease Modifying Drugs

Known diagnostic and prognostic biomarkers for AD [92] significantly enrich pathways involved in inflammation and immune regulation. AD biomarkers can be divided into two groups: 168 EOAD biomarkers [110][111] and 932 LOAD biomarkers [112][113]. There are 69 biomarkers that overlap between EOAD and LOAD: ACO2, ACTB, ACTG1,

ADAM10, ADIPOQ, ADRA1A, AIF1, APP, ANG, ACE, APOE, ABCA7, ATP6V1B2, ATP2A2, AURKC, AXL, BACE1, CACNA1G, CD33, CLP1, CLU, CR1, DICER1, DUSP13, DNMBP, FNDC5, GRK5, GBA1, GRN, H3C1, H3C10, H3C11, H3C12, H3C2, H3C3, H3C4, H3C6, H3C7, H3C8, IL1B, IL6, IL6R, KIF5A, HLA-DRA, MTHFR, MAPT, MBP, NSF, NDRG4, NRGN, NCSTN, NSUN2, PAK1, PLD3, PSEN1, RTN3, SLC10A3, SLC12A5, SLC24A4, SORBS2, SORL1, SPARCL1, TCIRG1, TYROBP, TREM2, TNF, YWHAG, VSNL1, and VWA2.

LOAD biomarkers led to more significant enrichments of immune system and allergic response pathways, apoptosis, tissue remodeling and repair, cell differentiation, cell cycle regulation, and neurofibromatosis [111], while EOAD led to more significant enrichments of heart failure pathway maps, stem cells, spermatogenesis, lipid biosynthesis regulation, and blood clotting pathways [111].

3. Artificial Intelligence and Machine Learning Approaches

Machine learning (ML) and artificial intelligence (AI) have been used successfully to extract insight from 'big' biological data [114][115][116]. Domain expertise from biology, genetics, elderly medicine, psychiatry, psychology, neurology, and neuroscience could be combined with new bioinformatics and statistical analytical tools to gain insight from multi-omics data. Such insight is valuable for providing answers for challenging research questions, and it can be achieved through the use of theoretical modeling [117][118]. In AD research, ML and AI can answer critical questions about combination diagnostic biomarkers, AD patient subgroups, and disease pathogenesis, thus supporting the identification of a personalized treatments for AD patients [119][120]. In fact, the use of AI has been suggested to probe the pathogenesis mechanisms of AD by analyzing big multi-omics data in parallel [121][122]. Additionally, AI has the capability to differentiate AD patients from other patients suffering from non-AD cognition impairment. It can also anticipate the progression from MCI to AD dementia and assign a tailored treatment for each individual patient [121]. Furthermore, the application of ML and AI approaches to AD research data, can lead to novel hypotheses regarding efficient interventions for AD patients [121]. AI can also aid in the diagnosis of the early stage of dementia [123].

Many research efforts focused on utilizing ML and AI approaches to mine data from clinicaltrials.gov records to evaluate anti-AD therapeutics in different stages of clinical development to study their mechanisms of action and important clinical trial characteristics [10][117][124][125][126][127][128]. AI and ML approaches can lead to important discoveries by learning from the recent advances in clinical trials and anti-Alzheimer's drug development pipelines [129][130][131][132][133][134]. Complex AI-based models could be exploited to inform researchers and health care providers about diverse disease etiologies, effective diagnostic biomarkers [120], and individualized treatments based on network biology approaches [135][136].

4. Exploring Epigenetic Treatments

Studies showed that DNA methylation/hydroxymethylation is dysregulated in AD patients prior the onset of clinical symptoms [11]. These were presented in a prospective study on autopsied brains, as level of methylation, in terms

of 5mC levels, in presymptomatic patients is similar to those with AD patients [137]. The levels of 5mC, 5hmC, and ten–eleven translocation 1 (TET1) proteins were elevated in preclinical AD patients and AD patients compared with the control group [138][139]. Although further validation is required, DNA methylation/hydroxymethylation may be used as a biomarker for AD diagnosis [11].

Histone modifications, particularly acetylation, deacetylation, and methylation dysregulation, play a role AD pathogenesis [11]. HDACs are highly expressed in patients with AD [138][140], affecting learning, memory, and cognition; hence, HDAC inhibitors (HDACi) are considered a potential treatment option [141]. Studies on AD patients showing low histone acetylation were reported [139][142][143], allowing the potential use of histone acetyltransferases (HATs) [139]. Increased levels of histone methylation and histone methyltransferase enzyme mRNA were reported in postmortem brains of AD patients [11][140]. Although the loss of histone methyltransferase function would affect learning capabilities in AD patients [11], the use of partial histone methyltransferase inhibitors [139] would restore the balance between histone methylation and demethylation in patients with AD to maintain brain integrity and memory [144]. Inhibitor of histone acetyltransferases (INHAT) is reported to bind to histones and block their access to HATs [145]. Studies showed that ANP32A, which is a component of INHAT and inhibitor of protein phosphatase-2A, is upregulated in AD patients [146][147]. In an in vivo study, the down regulation of ANP32A would reduce INHAT formation and allow for histone acetylation [148]. Collectively, drugs from those classes would comprise potential therapeutic options for AD treatment.

HDACi are considered to be non-selective [149], but they are beneficial, as they reduce AD hallmarks [143]. The use of HDACi that selectively inhibits HDAC2 and HDAC3 would improve cognition, in contrast to inhibiting HDAC1 that would result in neurotoxicity [11][143]. HDAC6 selective inhibitors were also shown to have neuroprotective effects [150][151]. Sirtuins, which are a class of HDACs, contribute to AD pathogenesis and selective inhibitors would also be beneficial [151][152]. Although some HATs showed better response than non-selective HDACi, their low membrane permeability and solubility limit their use in AD treatment [11].

The miRNAs are responsible for the regulation of gene expression through post-transcriptional gene silencing [153]. In relation to AD, several studies summarized by Nikolac Perkovic et al., 2021 [11] showed that miRNAs would be either downregulated or upregulated, altering proteins and enzymes expression responsible for AD pathology. Hence, the use of miRNA mimics to downregulate the expression of genes or proteins [154] or anti-miRNA therapies to alter the function of a specific miRNA [155] are also considered potential treatment options for AD patients.

5. Genetic Treatments

Targeting genetic alterations in AD patients and consequent gene editing and correction is another potential treatment strategy. These include the use of programmable nucleases, such as zinc finger proteins (ZFP), transcription activator-like effectors (TALE), and RNA-guided clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) [156]. The latter showed more promising results for AD treatment and other neurological diseases than did ZFP and TALE [157][158][159]. The presence of the mutant Cas9 protein, dead Cas9 (dCas9), advanced the CRISPR/Cas9 editing tool, resulting in the emergence of CRISPR

interference (CRISPRi) and CRISPR activation (CRISPRa) technologies, in which dCas9 is fused or interacts with transcriptional repressors or activators, respectively [160]. With regard to epigenetics, AD, and dCas9 protein, studies showed promising results with targeting histone demethylase [161], histone acetyltransferase [162], and histone methyltransferases [163][164].

6. Non-Pharmacological Treatment Options and Preventive Measures

Non-pharmacological treatments encompass several recommendations for various lifestyle modifications, including physical and social activity, tobacco cessation, alcohol consumption, weight management, nutrition, and regular exercise. Other interventions include underlying-disease management (e.g., hypertension, diabetes, dyslipidemia, depression, and hearing loss), as stated in WHO guidelines [165]. More studies should assess the relationship between vaccines and AD; it was found that flu vaccines reduce the risk of AD development [166]. However, the protective mechanisms have not yet been elucidated.

Aberrations in the ecosystem of microbiome have been implicated in diverse gastrointestinal and metabolic dysfunction, such as diabetes, insulin resistance, obesity, and inflammatory bowel disease [167]. In addition, studies showed that changes in gut microbiome is associated with neurological disorders, such as multiple sclerosis (MS), autism, and Parkinson's disease [168][169][170]. Studies recorded a decrease in microbial diversity in gut microbiome of AD patients [171][172][173][174][175][176][177][178]. Further studies in rats suggested that alterations in gut microbiome might proceed Aβ deposition [179].

7. Special Considerations for Clinical Trials

Aspects to be considered when designing a clinical trial include trial rationale, outcomes of interest, statistical analysis design, sample size and recruitment, and interim monitoring [180]. Common clinical trial designs include single-arm trials, placebo-controlled trials, crossover trials, and factorial trials [181]. In AD-related clinical trials, infrastructure and technology, cultures and linguistics, regulatory and reimbursement issues, academia and industry harmonization, availability, and access were considered to be the ultimate challenges that limit the conducting of successful clinical trials [182].

According to NLM's ClinicalTrials.gov Beta (beta.clinicaltrials.gov), 109 clinical trials related to AD were terminated in the last ten years [19]. AD clinical trials were terminated due to the following reasons: unavailability of further funding, halted visits due to COVID-19, feasibility of enrolment, safety issues, slow recruitment of eligible participants (patients), inappropriate study design to achieve the trial's endpoint, new safety or efficacy data from other studies, unfavourable risk–benefit ratio, and inappropriate dosage settings. Yet, patient recruitment remains the ultimate determinant in AD clinical trials.

Therefore, there is a need for new and advanced clinical trials designs to accelerate passage through the legal authorities' requirements to register new promising molecules for treatment and/or prevention of AD. However, new

investigation approaches need to be fully validated before they can be implemented in clinical trials [183].

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