" REPURPOSING ANTICANCER DRUGS FOR ALZHEIMER'S DISEASE:

A COMPUTATIONAL INTELLIGENCE PERSPECTIVE"

A DISSERTATION

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DECLARATION

I, Mugdha Sharma, 2K23/MSCBIO/67 student of M.Sc. Biotechnology hereby declares that the Dissertation Project entitled " REPURPOSING ANTICANCER DRUGS FOR ALZHEIMER'S DISEASE: A COMPUTAIONAL INTELLEGENCE PERSPECTIVE " is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science. This work is original and not copied from any source without paper citation. I have honored the principles of academic integrity and have upheld the normal student code of academic conduct in the completion of this work.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the Dissertation Project titled " Repurposing Anti Cancerous Drugs for Alzheimer's Disease: A Computational Intelligence Perspective " which is being submitted by Mugdha Sharma 2K23/MSCBIO/67, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science is a record of the work carried out by the student under my supervision. To the best of my knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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REPURPOSING ANTICANCER DRUGS FOR ALZHEIMER'S DISEASE: A COMPUTATIONAL INTELLIGENCE PERSPECTIVE"

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ABSTRACT

Aim:- Alzheimer's disease remains an urgent as well as unsolved neurological disorder of our time. It continues to be a worldwide health challenges as it is a progressive neurodegenerative disease that predominantly affects memory and cognitive function, marked by neronal death and tissue loss that span throughout the brain. Discovering therapeutic drugs for this disease is often complex due to it's intricate mechanism and rapid progression over patient's lifespan. Traditionally developing pharmaceuticals for AD often take prolonged development process, excessive cost, have high failure rate, off atrget delivery. Thus, drug repurposing, a promising approach to accelerating drug development is the inferring new therapeutic uses for existing drugs, which are already approved for incorporation into medication. Especially the role of, anticancer drugs and their potential in modulating several overlapping molecular mechanisms implicated in both cancer and AD.

This paper covers the recent advancement in AI, ML algorithms that accelerate the drug discovery and repositioning process to combat Alzheimer's Disease and identifying novel therapeutic target. In addition to improving early-stage drug development, these technologies also make it possible to repurpose existing drugs, such as anticancer agents, for Alzheimer's treatment.

Result: -As computational frameworks advance with revolutionary invention of "Artificail Intelligence"(AI) and "Machine Learning"(ML), the process of identifying, prioritizing, and validating such repurposable candidates has been revolutionized. This review highlights the transformative role of AI/ML in mining multi-omics data, predicting drug-disease associations, and evaluating therapeutic efficacy in silico. Key computational platforms, models, and case studies are discussed, with a focus on anticancer agents repositioned for AD. The findings underscore the synergistic potential of integrating computational intelligence with biomedical insights to both diseases provide an opportunity to somehow invent novel, precise and accurate therapies against them.

Conclusion:- The convergence of oncology and neurodegeneration has opened a promising frontier in the search for therapies for Alzheimer's disease (AD). Drugs such as **Palbociclib**, Tomoxifan, Dastainib, **Niraparib**, and **Tofacitinib**, etc originally developed for treating malignancies, have demonstrated potential neuroprotective function in AD models. With the advancement of computational frameworks, AI, ML and many other deep learning models have proved to be a saviour in hastening the drug developement process

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATION

AI	Artificial Intelligence
ML	Machine learning
DL	Deep Learning
ANN	Artificial Neural Network
VS	Virtual Screening
AD	Alzheimer's disease
Aß	Amyloid beta
PDB	Protein Data Bank
GEO	Gene Expression Omnibus
3D	Three Dimensional
ADME-T	absorption, distribution, metabolism, and excretion—toxicity
DTI	Drug Target Interaction
FDA	US Food and Drug Administration
PPI	Protein-Protein Interactions
HTS	High Troughtput Screening
QSAR	Quantitative Structure Relationship
SMILES	Simplifies molecular input line entry system
SAR	Structure activity relationship
GWAS	Genome-wide association studies
TCGA	The Cancer Genome Atlas
I-TASSER	Iterative Threading ASSEmbly Refinement
SCREEN	Surfacr Cavity REcognition and EvaluatioN
RF	Random Forest
RO5	Lipinski's rule of five
HTS	High Throughtput Screening
LGBM	Light Gradient Boosting Machine
PAINS	Pan Assay Interference Compound
CIAT	Compounds Interfering with Assay Technology
DTI	Drug Target Interaction
SOM	Self-Organized Maps
WOMBAT	World Of Molecular BioActivity
KG	Knowledge Graph
RNN	Recurrent Neural Networks
GAN	Generative Adversarial Networks
RANC	Reinforced Adversarial Neural Computer
LSTM	Long Short-Term Memory
RLSE	Reinforcement learning for structural evolution
PED	Predicter Encoder Decoder
GNC	Generative Network Complex
SBVS	Structure Based Virtual Screening
LBVS	Ligand Based Virtual Screening

kNN	k-Nearest Neighbour
GPCR	G-Protein coupled receptors
LOAD	Late Onset of Alzheimer's Disease
ROS	Reactive Oxygen Specie
NDD	Neurodegenerative diseases
PIN	Protein Interaction Network
NFT	Neurofibrillary Tangles
CAA	Cerebral Amyloid Angiopathy
AChE	Acetylcholinesterase
ACh	Acetylcholine
MAP	Microtubule associated protien
Cdk	Cyclin dependent kinase
GSK-3	Glycogen Synthase Kinase-3
LOAD	Late Onset of Alzheimer's Disease
IGF	Insulin Growth Factor
LDL	Low density Lipoprotein
NCBI	National Center for Biotechnology Information
SNP	Single Nucleotide Polymorphism

1. **INTRODUCTION**

Alzheimer's disease (AD) is a complex and progressive neurodegenerative condition marked by the buildup of amyloid-beta (Aβ) plaques and the abnormal phosphorylation of tau proteins, which results in neurofibrillary tangles, neuronal loss, and gradual cognitive deterioration.. It primarily affects memory causing dementia, cognitive impairment, major tissue loss that spans throughout the brain. As a result, the brain shrinks dramatically, declining the health and quality of life of patients suffering from AD. AD cases continues to rise exponentially with an estimate of nearly 510 million individuals worldwide being affected by 2050.[1] poses a dooming threat on our healthcare system. Especially in India and other developing country, this burden is further exacerbated by lack of resources, lack of access to health care, and financial constraint. Discovering therapeutic drugs for AD is often complex due to the intricate mechanism and rapid progression of AD throughput patient's lifespan. Out of the ongoing 187 clinical trials for AD drug until 2023, only 78% are concentrated on drugs involved in disease modifying therapies, rest of them lacking even a proper drug target against AD.[2] These limitations highlight the need for innovative therapies and identification of novel drug and target against AD.

A growing approach in therapeutic development is drug repurposing, which involves finding alternative medical applications for established drugs—especially those, like anticancer agents, that already have well-documented safety profiles. This approach significantly reduces the time, cost, and error rate associated with conventional drug discovery pipelines. In addition to being anti cancerous, these drugs are believed to reduce neuroinflammation, exhibit neuroprotective function that can modulate the dysregulated cellular or genome activity in AD patients. Hence, anti-cancerous drugs are an excellent alternative used to treat AD.

There are often several obstacles associated with drug discovery and designing process like time consumption, excessive cost, off target delivery, low efficacy etc. Additionally, the large set of databases associated with AD like data from clinical trials, gene expression data, microarray, proteomics, genomics and from online repositories hamper the process of drug development making it a very complex and tedious task. Drug discovery process has been revolutionized by AI and ML algorithms. These models help in analyzing high dimensional data obtained from multiple sources, prediction of drug target interaction, identification of novel drugs and their respective targets and aid in many more processes. These advanced computational models play a key role in facilitates prediction of drug target pair with extreme precision, pharmacokinetic properties, network pharmacology, molecular docking, virtual screening etc. [3]

The convergence of AI, ML has created a paradigm shift in biomedical field of research and open up new avenues to analyze "Big Data" and identify potential anti cancerous drug with neuroprotective properties. Big data here refers to enormous piece of data that is difficult to analyze with traditional software and tools. One of the most important characteristics of big data in biomedical domain is size. Other characteristics associated with it are volume, variety and velocity, where volume refers to the magnitude of the data, variety refers to the heterogenicity of the dataset, velocity refers to the rate of generation of data and it's analysis.It is also defined by three key attributes: volume, variety, and velocity. Volume

indicates the sheer amount of data, variety reflects the diverse nature of data sources and formats, while velocity describes how quickly data is generated and processed.[4][5]. AI has devised new dimension reduction techniques for nonlinear data.

In the realm of drug discovery, pinpointing new therapeutic targets remains a fundamental yet challenging step due to the high costs and complexity associated with experimental validation. Currently, fewer than 400 human genes are known to serve as targets for FDA-approved drugs, highlighting the limited scope of traditional approaches[6]. To overcome these limitations, computational strategies have emerged as essential tools for predicting novel drug-target interactions. Drug repositioning, the practice of identifying new uses for existing drugs, offers a strategic advantage by leveraging compounds with known safety profiles, thus bypassing early-stage toxicity studies.[3] Among repositioning techniques, activity-based screening has yielded promising results, particularly in repurposing non-oncology drugs for cancer treatment.

There are some emerging evidences that strongly claim towards the overlap in molecular markers of cancer and AD. Although the two fatal diseases stand at the opposite spectrum of cell cycle [7], the former is marked by uncontrolled cell proliferation while the latter results in neuronal death. Yet the two diseases share common genetic and molecular pathway and markers, these common factors play a key role in identifying anti cancerous drugs that also modulate neurodegenerative pathway and works against AD.

AI, or Artificial Intelligence comprises of a broad field that is capable of forming systems that are efficient at performing tasks that typically requires human intelligence. It can be trained on the past data and large datasets to improve it's task performing ability like problem solving decision making, deciphering natural language. The main aim of AI is to simulate human cognitive process and mimic the patterns that form in human brain during these processes like learning, problem solving etc. On the other hand, another subset of AI is known as" Machine Learning"(ML). " Deep learning"(DL) is a type of machine learning that takes advantage of" artificial neural networks"(ANN) with multiple layers to analyse databases. [9]

The incorporation of these advanced computational model in field of medicine is in two ways, either virtual or physical. Virtual application here refers to use of ML/ DL to leverages complex mathematical algorithms to improve learning through experience. Machine learning (ML) techniques are increasingly applied in biomedical data analysis, typically falling into three main categories first is "**unsupervised learning",** which identifies inherent structures or patterns in unlabeled datasets; "**supervised learning"** comes after that, which uses labeled data to train models for tasks like classification and prediction; and lastly, "**reinforcement learning"**, which involves learning optimal actions through feedback in the form of rewards or penalties over time[10]

This review aims to recapitulate these above mentioned advanced databases that constantly being integrated to renew the field of drug repurposing and unlocking novel drugs and their potential interaction with target.

2. Pathophysiology of Alzheimer's

Clinically AD manifests as a gradually progressive form of dementia, accompanied by structural and functional form of brain alterations such as cerebral atrophy, neuronal cell death, reduces synaptic

integrity, neuroinflammation etc. The main hallmark of AD is the accumulation of extracellular toxic amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). [11]

The development of β-amyloid plaques is due to a mutation in amyloid precursor protein (APP) gene, which is linked with cerebral amyloid angiopathy (CAA) and haemorrhage, lead to inconsistent enzymatic cleavage of APP, a transmembrane protein, by β secretases (BACE1) and γ-secretases.[12]This persistent cleavage leads to the formation of Aβ peptides, which are 38 to 43 amino acid long, accumulate extracellularly and aggregate into senile plaques.Deposition of these plaques in between the nerve cell blocks transfer of signals from one cell to other cell at synapse and activates immune system cells, as a repercussion of this disturbance inflammation happens that ultimately kills cell.Hence the amyloid cascade hypothesis emerged, according to which Aβ accumulation initiates a pathological cascade that activates hyperphosphorylation of tau protein that causes NFTs to form (also called the tombstone of dead and dying neurons), and onset of this cascade ultimately leads to neuroinflammation and neuronal death. Tau normally supports microtubule assembly and stabilization through reversible phosphorylation, it is an axonal microtubule associated protein (MAP), but in AD, its dysregulation leads to insoluble filamentous deposits that compromise neuronal function. [13][1]

This is followed by astrogliosis and microglial cell proliferation. A key regulator for activation of microglial cells is “Triggering receptor expressed on myeloid cells 2 (TREM2)”. The mutation in TREM2 leads to late onset of AD (LOAD). Therefore, this could be a potential target in future therapies.[14].

Mainly there are two enzymes associated with hyperphosphorylation of tau, cyclin dependant kinase (Cdk5) and glycogen synthase kinase 3 (GSK-3), hence inhibitor of these two enzymes also can be used to treat AD.

Furthermore, the presence of Aβ plaques enhances the acetylcholinesterase (AChE) activity, this causes rapid breakdown of acetylcholine (ACh) causing neurotransmitter deficit. AChE may also interact directly with Aβ peptides causing it to alter its conformation and promoting its aggregation into plaques.[15][16]. Therefore, acetylcholinesterase inhibitors are widely used to treat AD symptoms like rivastigmine [17] ,donepezil [18], galantamine[19]and memantine [20].

3. Crosstalk between cancer and Alzheimer’s

Cancer and Alzheimer’s have become two of the leading causes of death in the world. Although there appears to be dispartate mechanism involved in both diseases, but Oncogenesis and Neurodegeneration often share salient connection between them. Cancer and Alzheimer’s stand at opposite end when it comes to behaviour of cells in these abnormal conditions: cancer is marked by uncontrolled cell proliferation, that is, escape of cell from the regulated cell cycle, and evade apoptosis, hence are considered immortal. Conversely, in AD there is rapid neuronal loss due to accumulation of toxic plaques and overstimulation of immune system. Therefore, these two fatal diseases are considered to be at the opposite end of the spectrum, cancer due to evasion of cell death and AD due to frequent cell death.[21][7],[22]. In sum, it can be said that cancer is caused due to gain of function mutation like, proto-

oncogene transform into oncogene and drives normal cell to become a cancer cell. Meanwhile AD is caused by due to loss of function mutation that causes loss of cells.[23]

3.1 Epidemiological Inverse association

Countless studies have supported the theory that AD and cancer share an inverse relationship with each other. For instance, if a person suffers from AD, his risk of developing cancer gets halved. Similarly, if a person has a history of cancer, there are very few chances of them suffering from AD and onset of dementia, in a meta report analyses the chances might be 11-35% lower. The chances of AD patients developing tumor is as low as 61% than non-AD patients. [22]. Therefore, it can be inferred that there is mutual protection in the cases of these diseases, i.e., molecular mechanism favoring cell proliferation and survival might play a key role in protection against neurodegenerative disease. This important piece of information forms the basis of repurposing anti cancerous drugs to unlock their neuroprotective mechanism.

Since the seminal updates on hallmarks of cancer by Hanahan and Weinberg, it can be inferred that many of these biomarkers might be overlapping in the molecular mechanism of the two diseases and make the patient more susceptible to the development and progression of the other disease. [24], [25]

One of the key markers to be noted here is dysregulation of Protein Kinases. PKs are classified under oncoproteins responsible for development and progression of cancer, and coincidentally their dysregulation is also observed in AD, especially in the abnormal hyperphosphorylation of tau protein, which leads to the formation of NFTs and consequently lead to the development of AD.

The “Wnt signaling” pathway, named after the integration site of the “wingless-type murine mammary tumor virus”, plays a pivotal role in numerous cellular processes such as embryonic patterning, cell orientation, organogenesis, and the preservation of stem cell pluripotency. Interestingly, while its abnormal activation is commonly observed in various cancers, promoting tumor growth, the same pathway is often found to be suppressed in neurodegenerative conditions like Alzheimer’s and Parkinson’s diseases, where it typically offers neuroprotective effects[26], [27]

Another enzyme that has been oppositely regulated is Pin1, it is a signalling molecule, it causes confirmational change in target molecule to alter their function. It plays a key role in regulating proline directed phosphorylation. Hence it helps in the regulation of cell cycle. In AD, Pin 1 is downregulated which results in impaired APP cleavage and accumulation of NFTs and amyloid beta. Meanwhile this enzyme is overexpressed in cancer cells and leads to tumorigenesis and proliferation. [28][29]

While this narrative of AD and cancer being inversely associated is popular, some studies have also shown that there might be several biological and pathological similarities which run parallel in both the diseases. For example, both diseases are prone to develop with increasing age factor. It is considered one of the main governing factors for onset of both diseases. [30]With aging the cell repair processes slow down and ultimately halt, which manifests in mitochondrial damage and dysfunction, cell death, transformation of normal cell into cancer cells, ROS accumulation, cellular senescence and inflammation due to telomere shortening.[31]

There are several shared comorbid factors like diabetes and metabolic dysfunction.[32], [33]Other shared factor that equally contribute to theonset includes, environmental and behavioural factors, markedly micronutrient status, dietary habits, exposure to sunlight, tobacco use, physical activity levels, and contact with heavy metals etc.[34]On the other hand, there are several genetic factors that are also dysregulated in both cancer and LOAD, like expression level and function of microRNA. [35]

3.2 Genetic Overlap

The most noteworthy genetic overlap in these two diseases is by the tumour suppressor gene p53 or TP53. It is a master regulator of cell cycle and apoptosis and is often called the "guardian of genome" by Lane, D. The loss of function mutation of this gene is a hallmark of oncogenesis. However, in case of AD, expression of p53 is upregulated in the neurons in proximity of the amyloid plaques, hence it could be said that th gene is not mutated but dysregulated. [36]This upregulation is caused by increase in transcription of p53 due to APP and Aβ. Due to this damage in p53 gene and the cell machineryfailing to keep the genomic integrity intact, the cells re-enter the cell cycle to recover the excessive damage. This re-entering of cells into the cell cycle is a hallmark of AD pathophysiology. In AD, p53 forms aggregates and interacts with the tau protein, this compels interaction mediates DNA damage in neuronal cells. Due to the characteristic disruption of tau protein in AD pathology, inhibits the activation of downstream target for p53 and impedes its nuclear translocation.[37] Thedisruption of microtubular network is responsible for this mislocalization of p53. The damaged tau proteins fail tomaintain the integrity of the nuclear membrane and leads to accumulation of p53 outside the cells which is observed in many AD brain scans.[38][39]

Amyloid precursor protein (APP) plays a significant role in promoting the aggressiveness of various malignancies such as lung, breast, colon, pancreatic, thyroid, and prostate cancers, as well as acute myeloid leukemia. It enhances cellular behaviors including proliferation, migration, and invasion by activating signaling cascades like AKT and ERK [45][46]while it might downregulate pathways like Notch signaling and MAP kinase phosphatase which leads to expansion of tumour growth in tissue[40][41]while it might downregulate pathways like Notchsignaling and MAP kinase phosphatase which leads toexpansion of tumour growth in tissue.[42]

Interestingly, the cleavage pattern of APP in neurodegenerative disorders such as Alzheimer's disease differs from its processing in cancers. In particular, insulin-like growth factor 1 (IGF-1) modulates APP and APLP2 cleavage by upregulating α-secretase activity, which influences their functional outcomes in both disease contexts[43]Therefore, targeting drugs that block IGF-1 can be a key modulator in cancer.

A gene that strongly contributes to the development of LOAD is APOE4 (Apolipoprotein E) that is often found in cells of central nervous system (CNS). It is a lipoprotein, that plays a key role along with its isomers in lipid homeostasis and cholesterol transport in cells, by acting as a ligand for binding with Low density lipoprotein receptors (LDL).[44] It has three isoforms, ApoE2, ApoE E3, and ApoE4 coded by alleles APOE ε2, ε3, and ε4 respectively and out of these three isoforms ApoE4 pose a big threat for development of AD. Hence it plays a monumental role in being a target for development of anti-amyloid drugs.[45][46], [47]There are also several observations that APOE might hamper the Wnt signaling, which is responsible for its neuroprotective function in AD.[48]

Although APOE4 was never suspected to play a role in cancer, its hidden influences were discovered later, that it influences both diseases by targeting lipid metabolism as well as immune response. In AD, APOE4 is responsible for the modulation of Aβ accumulation and clearance, while in cancer it directly targets immune response and alter availability of lipid. For instance, in prostate cancer, secreted APOE can induce senescence of infiltrating neutrophils, contributing to an immunosuppressive microenvironment. Meanwhile, in ovarian cancer, overproduction of APOE is linked to more aggressive and metastatic form of cancer, with APOE potentially inducing senescence in neutrophils. [47], [49] The APOE ε2/ε4 isoforms are associated with more advanced disease and higher cellular cholesterol retention.[50]In breast cancer, APOE ε2 might play a protective role against cognitive decline as a side effect of the chemotherapy received by the patients, while APOE ε4 carriers may be at greater risk of declining cognitive abilities and eventually developing AD. [47], [51]

Overall, it can be concluded that APOE has a more direct influence in AD, and it is heavily genetically driven in AD than in cancer. While its role in cancer is rather context driven affecting the immunoregulation.

3.3 Shared Molecular Pathways

Despite the accumulating evidence of AD and cancer being inversely related, they share many key regulatory pathways which are often disrupted in opposite direction.

Redox imbalance contributing to Oxidative stress, affects both diseases in distinct ways. ROS are a byproduct of aerobic metabolism and are generated in mitochondria during the electron transport chain (ETC). [52]However oncogenesis is marked by mitochondrial dysfunction, and exponential increase in amount of enzymes associated with ETC, i.e., NADPH oxidase, Cytochrome P450, Xanthine oxide etc, consequently the additional ROS are found in the cell, leading to tumour generation and proliferation.[53]Cancer cells not only damage the cellular cycle and escape checkpoints by modulating the genetic factors and growth cycle but by also creating a peculiar microenvironment around them that triggers immune responses, like hypoxia and inflammatory reactions, that leads to generation of more ROS. The excessive accumulation of reactive oxygen species (ROS) contributes to oxidative stress, which can induce genetic alterations in proto-oncogenes. Over time, this oxidative damage may initiate the transformation of healthy cells into malignant onesWhile progression of AD is marked by damage caused to neuronal cells by elevated levels of ROS, causing genetic instability and neuronal death. It is also found to impair the cell repair mechanism, so once the neurons get damaged there is no other way to revive them then halting their growth process and ultimately killing them. Like cancer, in AD an elevation of ROS is observed again due to mitochondrial dysfunction, but in this disease the manifestations are different. Generation of elevated level of ROS causes mitochondrial DNA to mutate, damage the ETC, disrupt the membrane permeability by damaging polyunsaturated fatty acids spanning the membrane, impaired stress resistance, metabolic flexibility, enhanced oxidative phosphorylation etc. [55], [56]The inconsistent expression of a cell cycle protein called Cyclin dependent kinase-5 (Cdk5) causesROS accumulation, the main culprit of DNA damage and mutation. [57]

Another hallmark of pathophysiology associated with AD is the extracellular deposition of amyloid plaques, intracellular tau proteins in which form an arbitrary mass of fibres, NFTsand sometimes α-synuclein, these clusters of protein further aggravate oxidative stress and inflammation.[58]Due to reoccurring hypoxia and inflammation, the calcium homeostasis in mitochondria gets disrupted. The combinatory effect of ROS and accumulation of toxic byproducts causes frequent death of neurons.[59]

Unchecked and uncontrolled cell cycle is a characteristic feature in both diseases, although the former caused rapid, unchecked proliferation of cells and latter invokes premature death of cells. Cell cycle comprises of 4 phases, G1 marked by cells preparing for growth, followed by S phase, which is dominated by DNA synthesis, G2 phase which is preceded by the actual division phase called the M phase. The engines that drive the progression of these stages are a series of protein complexes called: cyclin and cyclin dependant kinases (CDKs). Neurons in AD brains show an augmented attempt to increase these kinases (CDKs), oxidative and metabolic stress might be the possible trigger for these elevated levels. Meanwhile, cancer cells inactivate cell-cycle checkpoints, due to loss of function mutation in tumour suppressor genes to bypass these checkpoints and multiply unchecked. Thus, dysregulation of cell cycle is noted in both diseases. This paradox may arise because post-mitotic neurons cannot complete division, so cell-cycle re-entry triggers apoptosis via p53/p21 signalling. This ectopic re-expression of cell cycle proteins has let to this hypothesis of aborted re-entry disruption of cell cycle in particularly G2/M phase of cell cycle, of damaged neurons in AD. Regulatory proteins such as cyclins are essential for the timely transition between cell cycle phases[60]The key genes, AβPP, Presenilin 1, and Presenilin 2 (PS1/2) which are the main culprit in NDDs are also involved in cell cycle dysregulation.[61]

A signalling pathway that is considered to be the underlying mechanism to regulate cell growth, proliferation and apoptosis is the PI3K/Akt signalling pathway.[62]Due to metabolic stress or oxidative stress, the PI3K/Akt gene gets activated it leads tosubsequent activation of mTOR which is a kinase and considered as a central regulator of cell metabolism, protein synthesis and translation, autophagy, cell growth and survival. Hyperactivation of PI3K/Akt causes mTOR inhibition, which leads to accumulation of toxic compounds, plaques, peptides, misfolded proteins and causes neurodegeneration.[7], [63]

Autophagy which is termed as programmed cell death or cellular “self-cleaning” is another dysregulated process that an attribute of these two pathologies. In AD, elevated level of Aβ and tau is due to inactivated autophagy. By contrast, cancer cells often exploit autophagy for survival under stress. Therapeutically, promoting autophagy helps clear aggregates in AD models, whereas inhibiting autophagy can sensitize cancer cells to treatment. In sum, autophagic flux is a critical node: its failure in neurons drives AD pathology, while its modulation in tumours affects cancer growth.[7]

4. Application of AI, ML databases in drug discovery

Identification of pharmacologically active substance, in drug discovery pipeline, that has the ability to modulate the disease-causing target and combat the disorder, is the most daunting step. Historically, pharmaceutical research and development have concentrated on creating orally bioavailable small-molecule therapeutics that target well-characterized, druggable proteins. The foundation of this approach is encapsulated by Lipinski’s Rule of Five (Ro5), established in 1997 through analysis of the

physicochemical properties of compounds that reached Phase II clinical trials. These guidelines have since become a cornerstone for the rational design of small molecules in early-stage drug discovery.

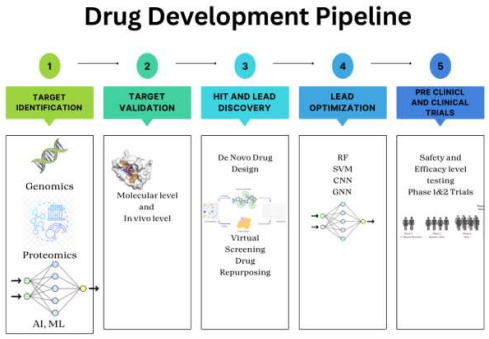

Fig1. Schematic representation of drug development

While targeting known druggable proteins using Ro5-compliant molecules has yielded significant therapeutic advancements, there is a growing need to explore previously intractable targets that could drive the development of next-generation therapies. In response, the scope of drug discovery has expanded to include molecular frameworks that lie beyond traditional Ro5 parameters. These include bifunctional molecules such as PROTACs (proteolysis-targeting chimeras), which facilitate targeted protein degradation, as well as other non-conventional modalities like PPI (protein–protein interaction) modulators, peptidomimetics, and oligonucleotide-based therapeutics. The focus has thus shifted toward innovating therapeutic strategies that not only conform to but also transcend the limitations of classical small-molecule design.

The development of drug for Alzheimer's and other CNS disorder is challenging, due to the failure of drug therapy to adapt to the progressive nature of CNS disorders, low efficacy, off target effects, inability to overcome blood brain barrier (BBB), expensive procedures and lab trials, several side effects etc. These factors hamper the traditional drug discovery and development process.

AL, ML has revolutionised the field of drug discovery and development, promising an alternative solution to these limitations. These AI, ML based models accelerate pharmaceutical research by analysing complex datasets, online repositories, big data, to find desired drug target by analysing its desired properties and chemical modifications, de novo drug synthesis, high throughput virtual screening, drug repurposing strategy etc. In other words, AI facilitates the elucidation of mechanisms of action, thereby enhancing the precision and efficiency of modern drug discovery processes.

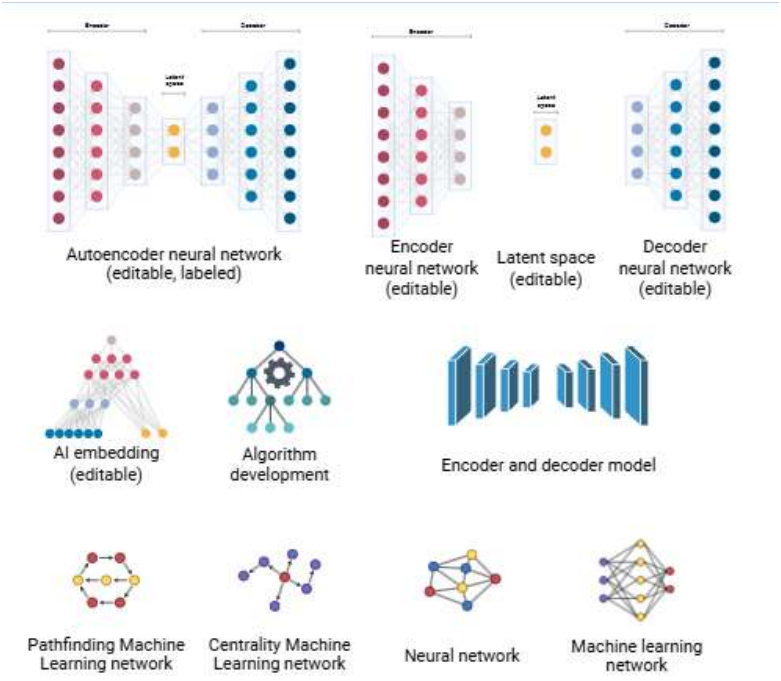

Fig 2. Representation of AI, ML models (Created in https://BioRender.com)

4.1 Target Discovery

The initial phase of drug discovery typically involves recognizing a new biological target, the regulation of which is expected to trigger a beneficial therapeutic effect without compromising patient safety. Following the identification, the novel drug target is validated either through vivo models and then proceeds to be tested in multiphase clinical trials. Consequently, the early recognition of pharmacologically relevant targets plays a critical role in determining the success of a drug development pipeline. The highly complex and layered nature of these extensive “Big data” reduce the efficiency of drug discovery pipeline but also opens up avenues of extracting novel information and discovering targets through application of advanced models. Big data refers to a type of complex multifactorial data with high dimensionality that needs to be reduced in to improve drug discovering efficacy, reduce undesired results, improve the accuracy of search results, data visualization and high data compression.[4]To reduce this dimensionality of this nonlinear and complex dataset, multiple methods are employed. Deep auto encoder is one amongst them, it is a technique that encompasses a multilayer encoder sub-network responsible for transforming high-dimensional data into a condensed low-dimensional data, as well as a corresponding multilayer decoder sub-network tasked with reinstating the original high-dimensional data from the derived low-dimensional abstraction.[64], [65], [66]

An ideal drug target exhibits many quality traits like appropriate druggability, i.e, its ability to modulate disease target with minimal adverse effects. Many machine learning and deep learning models, in particular, have been implemented to access this complex data and extract meaningful targets from it.

In the process of target identification, two steps need to be completed to conclude with a relevant and effecient target of the disease, these steps are firstly the target is discovered and then the it is deconvoluted[67]The former involves the identification of new disease-associated targets that are amenable to therapeutic modulation. The latter refers to the process of elucidating the molecular target of a compound with known bioactivity, often termed "target fishing." Both approaches are vital components in the early-stage development of novel therapeutics.

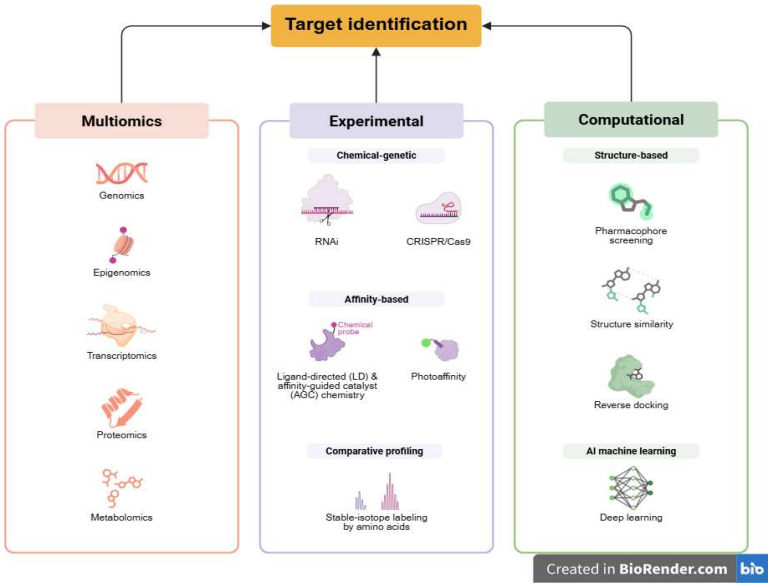

Fig 3. Schematic diagram of incorporation of AI, ML computational models and convention steps in target identification step (Created in https://BioRender.com)

Advances in artificial intelligence have facilitated the development of sophisticated techniques for dimensionality reduction, particularly for complex, non-linear datasets. Among these, deep autoencoders, structured as multi-layered neural networks, have proven to be highly effective in extracting lower-dimensional representations while preserving essential data characteristicsThis technique encompasses a multilayer encoder sub-network responsible for transforming high-dimensional data into a condensed low-dimensional representation, as well as a corresponding multilayer decoder sub-network tasked with reinstating the original high-dimensional data from the derived low-dimensional abstraction.

Firstly, to identify the suitable target to modulate the disease or abnormal gene expression, we need to analyse the gene expression data gathered from various elaaborate experiments, as well as from online repositories, like NCBI “Gene Expression Omnibus (GEO)”,which is one of the most widely searched platform for retrieving gene expression data. This platform is a critical tool for storage and dissmination of high throughput genomic datasets, obtained from microarray, next generation sequencing, research-oriented data, RNA Seq data etc. [68]Target identification facilitated by GEO involves, first the

comparison of differential gene expression between diseased and normal conditions, and then identification of dysregulated genes and signalling pathways that might include this identified therapeutic targets. Shortlisting of these target candidate is based upon the fulfilment of multiple criteria like specificity towards a certain disease, expression dynamics in both diseased and normal cell, potential druggability, toxicity, responsiveness to drug candidates etc.[69] Another gene expression data repositories include The "Cancer Genome Atlas (TCGA), [70]Arrayexpress etc.[71] These online repositories also offer extensive transcriptomic datasets applicable to various disease contexts.

In parallel, Genome-Wide Association Studies (GWAS) provide a complementary strategy for elucidating the genetic expression data of complex diseases. GWAS facilitates in analysing th whole genome of an individual, to observe whether certain genetic variants with associated diseases are recurring. In other words, GWAS scans the entire genome of the organism and identify the position of single nucleotide polymorphism (SNPs). Analysing this data gives us an insight on the genetic pattern of inheritance of the disease target gene, and the future risk of an individual of inheriting that gene.[72]Databases like GWAS Central [73]and the NHGRI-EBI GWAS Catalog[74]aggregate and curate genomic variant data, allowing researchers to associate specific loci with disease susceptibility. These loci often highlightgenes that can be considered as a functional target in disease development, therefore offering an avenue to target and modulate the expression of that loci by drug candidate thereby facilitating advancements in personalized medicine.[9]

An example of AI-driven innovation in this domain is PandaOmics, which is a computational platform designed to integrate multi-omics datasets and literature mining to identify novel drug targets. In a recent application to idiopathic pulmonary fibrosis (IPF), PandaOmicsidentified USP1 (ubiquitin specific peptidase 1) as a previously unrecognized yet disease-relevant target. This discovery, which emerged from AI-based inference rather than conventional knowledge, exemplifies the power of artificial intelligence in uncovering hidden biological associations. The identification of USP1 ultimately led to the development of a novel small-molecule inhibitor (INS018_055), which entered clinical evaluation in 2023. [75]

The identification of such disease-related genes is largely enabled by the analysis of high-throughput genome and exome sequencing data. Public databases like the Sequence Read Archive (SRA) (NCBI SRA) serve as a central repository for raw sequencing data generated through next-generation sequencing (NGS), supporting comprehensive exploration of genetic alterations relevant to disease pathophysiology. Cancer-focused genomic resources, such as the "Genomic Data Commons (GDC)" and "The Cancer Genome Atlas (TCGA)", [76]offer curated sequencing datasets that enable researchers to identify oncogenic mutations and dysregulated pathways with potential therapeutic implications. Similarly, traditional repositories such as **PubMed** (https://pubmed.ncbi.nlm.nih.gov) provide extensive access to peer-reviewed biomedical literature, facilitating data mining for target validation and pathway analysis and ChEMBL (https://www.ebi.ac.uk/chembl) offers a vast collection drug like compunds, annotated with pharmacokinetic, pharmacodynamic, and toxicological data. **DrugBank** (https://go.drugbank.com) integrates molecular data on drugs, their biological targets, mechanisms of action, and clinical use, supporting drug repositioning and interaction analyses.

Structural biology tools are equally critical in modern drug discovery. The **Protein Data Bank (PDB)** (https://www.rcsb.org) provides open access to experimentally determined three-dimensional structures of

biomolecules such as proteins, DNA, and RNA, which are extensively used to study protein–ligand interactions and guide rational drug design through structure-based approaches. Integrating the cancer genome research and ML database, a DriverML (https://github.com/HelloYiHan/DriverML) tool was developed, based on supervised learning it helps in accessing cancer driving genes and identifying them as a potential target.[77] A brand new AI model called BenevolentAI has been created to construct knowledge graph to identify and concentrate the desired area of drug-target interactions to identify drug candidates especially Janus kinase inhibitors (JAK) in this case, that can be repurposed. This AI model has been used to identify novel drugs that target SARS COV-2 virus. However, with the continuous evolving nature of these AI platforms it can be applied to find targets in AD, Cancer etc. [78], [79]

For Alzheimer's disease (AD), several disease-specific omics repositories have been established to advance target identification. The **AMP-AD Knowledge Portal** (https://adknowledgeportal.synapse.org) offers high-quality multi-omics data (genomic, transcriptomic, proteomic) from human brain tissues and animal models, generated under NIH-funded initiatives. **AlzData** (http://www.alzdata.org) integrates multi-omics information to support target prioritization, pathway mapping, and prediction of drug-gene interactions in AD.Additionally, **AlzGPS** (https://alzgps.lerner.ccf.org) combines multi-omics data with protein interactome networks and drug repurposing frameworks to uncover therapeutic strategies for AD.

Artificial intelligence (AI) is increasingly transforming the landscape of drug development. Currently, more than 150 drug candidates powered by AI technologies are undergoing either the discovery phase or preclinical evaluation across various therapeutic areas. This trend highlights the expanding role of computational methods in streamlining target identification and optimizing drug development pipelines.[80]

4.2 Target Prioritization

Target prioritization refers to the process of evaluating and ranking potential biological targets (like genes, proteins, or pathways) that are involved in the pathology of a disease, in order to decide which ones are the most promising for therapeutic intervention. Not all discovered targets are: druggable, relevant to the disease, safe while being accessible to molecules at the same time. In order to combat this we usetarget prioritization to narrow down the list by evaluating features like: it's biological relevance ,Druggability whether modulating it can have therapeutic effects, Genetic support like it should have strong association with disease in GWAS and other gene expression analysis studies, Safety profiles, Expression of the selected target in relevant tissues, for relevance brain tissue here. Machine learning models accelerate this process by: - Integrating heterogeneous data (genomics, omics, literature, pathways) from multiple platforms, Predicting gene-disease relationships, Scoring and ranking targets, learning patterns from known successful/failed targets.[67]

There are many softwares and programmes for target discovery and prioritisation like iCLUE &ASK™, developed by Standigm. It is an AI platform that is employed in prioritize protein targets for diseases by constructing and evaluating a graphical database to rank targets based on various relevant categories.

As the demand for novel drug targets increases, the experimental validation of candidate targets remains a resource-intensive and time-consuming challenge. To address this, AI and ML methodologies have been employed to facilitate the prioritization of high-potential targets for downstream validation. For instance, a Support Vector Machine (SVM)-based classifier integrating multi-omic data such as DNA copy number variations, mRNA expression profiles, mutation frequencies, and protein–protein interaction (PPI) networks, was developed to predict and rank candidate targets specific to breast, pancreatic, and ovarian cancers. [81]

An alternative strategy for target prioritization involves integrating multiple networks of gene interactions and utilizing a kernel-driven machine learning approach to rank genes according to disease-related MeSH annotations..[82]

Further advancing this area, data from the online repositories is extracted to train a semi-supervised neural network model, which facilitated the identification of previously unrecognized therapeutic targets. [83]Additionally, biomedical literature resources such as Medline have beenutilized for predictive modelling; the tool DigSee employs natural language processing (NLP) and Bayesian classification to extract disease–gene relationships from textual data and ranks them based on evidential strength. [84]In another approach, implemented three positive-unlabelled learning algorithms are used to predict and prioritize over 3,000 genes potentially implicated in human aging.[85]Their model incorporated binary gene features derived from 11 human biological databases to assess the relevance of each gene in the context of age-related processes. AI-powered knowledge graphs are employed to integrate diverse biomedical data sources, enabling efficient prioritization of genes related to the immune system for AD research. This accelerated the evaluation of 54 genes from several weeks to days, facilitating faster identification of potential drug targets for laboratory testing.An AI-driven, network-based approach combines genome-wide association study (GWAS) findings, multi-omics datasets, and the human protein interaction network to identify potential drug targets influenced by genetic variants linked to Alzheimer's disease.. It identified 103 AD risk genes validated through various levels of pathobiological evidence, providing a robust set of targets for therapeutic development.. [86]

Insilico Medicine has developed **PandaOmics**, an advanced artificial intelligence and machine learning (AI/ML)-based platform for therapeutic target discovery. This system is designed to analyze gene expression dysregulation and pathway alterations across heterogeneous datasets associated with **amyotrophic lateral sclerosis (ALS)**. By integrating over 20 distinct ML and bioinformatics models, PandaOmics ranks potential therapeutic targets based on parameters such as disease association strength, druggability, developmental maturity, and tissue specificity. [75]

A distinguishing feature of PandaOmics is its application of "**graph-based neural networks" (GNNs)**, which offer advantages over traditional architectures. Unlike non-graph models, GNNs can natively incorporate biological network topologies, allowing the model to learn node embeddings that encapsulate relational and contextual information within protein or gene interaction graphs. This facilitates accurate biological inference by analyzing connectivity patterns in cellular systems (Hamilton et al., 2017).

Protein-protein interactions (PPIs) are central to nearly all cellular processes, as proteins rarely act in isolation but instead form dynamic and complex networks of interactions. Understanding these PPIs is critical for elucidating cellular function and disease mechanisms. Computational methods offer a time-

and cost-efficient alternative to experimental approaches in PPI prediction, especially when leveraging structural and sequence-level protein data.

In a notable study, a graph-based deep learning approach combining "**Graph Convolutional Networks" ("GCNs")** for predicting PPIs. The authors constructed residue-level protein graphs using three-dimensional atomic coordinates derived from **Protein Data Bank (PDB)** files. Each node in the graph represents an amino acid residue, and an edge is defined if atoms from two residues are within a pre-specified distance threshold. Node features were extracted using **pre-trained protein language models**, which convert the primary protein sequence into contextual embeddings for each amino acid.[87]

Their methodology was validated using PPI datasets from *Homo sapiens* and *Saccharomyces cerevisiae*, achieving superior performance relative to previous state-of-the-art methods. These findings highlight the potential of GNN-based frameworks in biological network modelling and their application in AI-driven drug discovery workflows.

4.3 Target Protein Structure Prediction

Accurate prediction of protein structures plays a pivotal in drug discovery, as the 3-D conformation of a protein dictates its function and interaction with potential therapeutic drugs.Conventional techniques such as X-ray crystallography and cryo-electron microscopy offer high accuracy but typically require significant time and resources to carry out. Recent advancements in artificial intelligence (AI) have revolutionized this domain, offering rapid and reliable computational approaches to predict protein structures, thereby accelerating the drug development process.[88]

AlphaFold, an artificial intelligence tool created by DeepMind (a subsidiary of Google), has revolutionized protein structure prediction. This system, particularly AlphaFold 2 introduced in 2020, set a new benchmark in accuracy during the CASP14 evaluation, reaching a median Global Distance Test (GDT) score of 92.4—approaching the precision of experimental methods. Its impact has been profound, dramatically increasing the number of known protein structures. Today, the AlphaFold Protein Structure Database contains structural data for more than 200 million proteins, covering much of the known protein space[94] , achieving a median Global Distance Test (GDT) score of 92.4 across all targets, indicating near-experimental accuracy. This advancement has significantly expanded the structural coverage of the protein universe, with the AlphaFold Protein Structure Database now encompassing over 200 million protein structures. [67], [89]. By combining AlphaFold's structural predictions with AI-driven drug design platforms based on the evolutionary, physical and geometrical constraints of the protein, they achieved the goal within a remarkably short timeframe.

AlphaFold predicts the three-dimensional structure of proteins from their amino acid sequences and aligned homologous sequences. It combines the power of biological data with advance AI models and deep learning algorithms to predict accurate structures. This is achieved through the integration of two primary strategies: first, the extraction of conserved, co evolutionary sequence domains from multiple sequence alignments to infer spatial proximity between amino acid residues, and secondly, the application

of deep neural networks (DNNs) to model these co-evolutionary dependencies and translate them into protein-specific statistical energy landscapes.[67], [90] Among ab initio structure prediction methods, AlphaFold hasdemonstrated unprecedented levels of accuracy, often approaching experimental resolution. Moreover, AlphaFold 3, the latest iteration, extends its predictive capabilities to encompass protein interactions with DNA, RNA, and small molecules, thereby providing a comprehensive framework for modelling complex biological systems and facilitating structure-based drug design. [89], [91]

Apart from AlphaFold, other AI based tools like **I-TASSER** (Iterative Threading ASSEmbly Refinement) are also being used to predict the structural features of a protein, it adopts a hierarchical protocol combining threading, ab initio modelling, and atomic-level structural refinement to forecast both protein conformation and functional annotation[92]RoseTTAFold, created by the Baker Lab, utilizes a ”three-track neural network” design that concurrently processes sequence data, spatial distances, and atomic coordinates[93]

A DeepFragLib, a fragment library was developed by integrating the strengths of AlphaFold and DL algorithms, to fine tune the protein structure prediction.[93]Despite these advancements in protein structure prediction, challenges persist in accurately modelling intrinsically disordered regions, conformational flexibility, and post-translational modifications. Future research aims to enhance the dynamic modelling of proteins, integrate multi-omics data, and improve the prediction of protein-ligand interactions to further refine drug discovery processes.

4.4 Target Evaluation

Target evaluation comprises of careful and confident assessment of whether a biological molecule is a good candidate for drug development. In the process of target discovery, assessing the druggability of a biological target, defined as its potential to be modulated by small-molecule therapeutics, is pivotal. [94]A viable drug target must exhibit specific biophysical attributes that enable effective binding to drug-like molecules. The integration of machine learning algorithms has significantly advanced drug evaluation process, particularly in discriminating between functional classes such as druggable versus non-druggable proteins. A wide array of algorithms—including SVMs, decision trees etc—have been widely utilized for these tasks.

The availability of high-quality "omics" datasets, coupled with improvements in computational methodologies, has led to the proliferation of ML-based predictive models for target prioritization and evaluation. Given the long, costly, and low-success nature of drug development, achieving high-confidence validation at early stages is imperative. Early identification and prioritization of promising targets are crucial to enhancing the overall success rate of drug discovery pipelines. In recent years, pharmaceutical industries have increasingly incorporated computational models—particularly machine learning frameworks—at the initial stages of drug development. These models exploit features such as sequence composition, biological network connectivity, structural characteristics, gene expression profiles, and subcellular localization to capture the essential attributes of successful drug targets and predict novel candidates with analogous properties.

An example of integration of ML, is the SCREEN (Surface Cavity REcognition and EvaluatioN) web server. [95]which utilized a Random Forest (RF) classifier trained on the geometric, structural, and physicochemical properties of protein cavities known to either bind or not bind small molecules. These analyses demonstrated that the surface cavity size and shape are among the most influential factors in determiningdruggability. Subsequent studies expanded the use of ML techniques, including Support Vector Machines (SVMs), for predicting druggable proteins based on various sequence-derived physicochemical features. Dezső and Ceccarelli, for instance, developed RF-based models specifically for oncology targets,and then to shortlist drygs based on their similarity score. [96]

4.5 Target Validation

Following the identification of a potential drug target, it is crucial to validate its functional role within the disease context. Traditionally, antisense technology has been extensively utilized for this purpose. In this method, short single-stranded oligonucleotides are designed to complement specific sequences within the target messenger RNA (mRNA), thereby binding to it and disrupting translation, ultimately inhibiting the synthesis of the corresponding protein. Conditional knock-out strategies provide another important tool for target validation. Unlike conventional knock-outs that often result in embryonic lethality and developmental defects, conditional knock-outs allow for temporal and tissue-specific gene inactivation, minimizing associated risks and offering a refined approach to study gene function.

Target validation involves confirming that the identified biomolecule—whether a gene, protein, or nucleic acid—directly contributes to the disease mechanism and can be modulated effectively by therapeutic agents. Several strategies are employed in this process, including structure-activity relationship (SAR) studies of small-molecule analogues, knockdown or overexpression geneticexperiments, and monitoring alterations in downstream signalling pathways influenced by the target. While validation using disease-relevant cellular and animal models provides critical evidence of a drug candidate's efficacy and toxicity, the definitive assessment of target validity is ultimately determined through clinical trial outcomes.[97]

4.6 Hit Identification and Structural Insights in Drug Design

Following the validation of a therapeutic target, the subsequent phase in the drug discovery pipeline involves the identification of *hit compounds*—defined as chemical entities that demonstrate the intended biological effect in a screening assay. A variety of methodologies are employed for hit discovery, among which **High Throughput Screening (HTS)**remains a prominent experimental approach. It enables the rapid assessment of extensive compound libraries, containing millions of drug like compounds, against the target of interest. Screening may be carried out using **biochemical assays**, where purified target proteins are utilized, or **cell-based assays**, especially when target modulation leads to detectable cellular responses and to identify ligand receptor affinity. A critical prerequisite for these strategies is the establishment of **biologically relevant assays** to evaluate compound efficacy. Once initial hits are identified, a conventional downstream strategy involves **co-crystallization** of the candidate compound with the target protein. The resulting **X-ray crystallography** data provides high-resolution structural insights into the protein-ligand interaction, particularly the architecture of the binding pocket. These

insights form the basis for **structure-based drug design** and hit-to-lead optimization.Additionally, **drug repurposing**, also called drug repositioning, is as a viable strategy to uncover novel therapeutic applications for existing approved drugs. This approach significantly reduces the developmental timeline and associated risks. In support of rational drug design, **network-based models** have been widely applied, integrating various biological and pharmacological datasets.[97]

4.7 Identification of lead and Hit to Lead optimization

A chemical lead refers to a molecule that is synthetically accessible, stable, and exhibits drug-like propertiesFor instance, Khan *et al.* gathered ~2,500 AChE inhibitors (2,037 actives, 501 inactives from ChEMBL) and generated PubChem fingerprints. They trained RF, SVM and neural-network models using cross-validation, finding that the RF classifier outperformed SVM with former having 94.1% accuracy, MCC=0.85 and the laterbeing 90.1% accurate . The RF model was then used to screen a 51K-compound library (Maybridge), yielding 922 candidates with >90% predicted activity. These hits were further filtered by molecular docking to AChE, and top-scoring compounds were subjected to MD simulations. This RF/SVM model aided the screening process of almost 1000s of drug candidate scored by ML and further filtered them out by molecular docking to give 4 promising lead compounds. [98]

A ligand-based ML pipeline to find Aβ fibril binders was built for hit identification. They used a three-step workflow comprising of property filter + 2D descriptor model + 3D field-point models which screened ~698 million ZINC compounds. Out of all 100 predicted binding leads, 46 were tested, yielding 5 novel Aβ ligands with Kd = 20–600 nM (hit rate ~10.9%). This study combined a simple ML regressor with 3D shape models, demonstrating ML's power to identify entirely new scaffolds against AD pathology.[99]

Similar ligand-based ML approaches have been applied to BACE1, tau aggregation, etc. For example, Das *et al.* (2023) used an AI-driven tool (PyRMD) to virtually screen ZINC compounds for tau-aggregation inhibitors. This reflects the broader trend of integrating AI with docking and MD to prioritize hits. [100]Beyond in silico screening, ML is transforming experimental HTS workflows. Traditional HTS tests large libraries blindly which generally has hit rates less than 1%, but incoporating ML can make this process easier and more efficient. A prominent strategy is **iterative (active-learning) screening** in whicha small subset out of a large sample of compounds is screened experimentally, and a model like RF/SVM/LGBM/GNN is trained on those results. And this is repeated with another small subset.

Svensson *et al.* (2021) found out that even with as little as 35% of a library screened, iterative ML recovery of *known actives* was ~70% . Screening 50% of the library recovered ~80% of hits at a time. In other words, ML-guided screening found most actives with far fewer tests, saving time and cost. [101]Other ways ML can be used in HTS include hit triage and quality control. Many HTS hits might be false positives (assay artifacts, pan-assay interference compounds – PAINS). ML models can be trained to flag such *frequent hitters*. For example, AstraZeneca researchers built an ML classifier (using 2D descriptors) to predict Compounds Interfering with Assay Technology (CIATs). This model, trained on known CIATs vs non-CIATs, successfully identified artifact-prone molecules. Interestingly, the authors

noted that “well-curated datasets can provide powerful predictive models despite their relatively small size”, underscoring that even limited quality data enables ML to improve hit triage.

Finally, ML can extract hidden information from HTS data. In high-content imaging screens, ML has been used to **repurpose assay readouts**. In one study, features from a glucocorticoid-receptor translocation screen were used to predict compound activity in unrelated assays. Remarkably, this repurposing via ML **boosted hit rates by 60–250**× compared to the original screens. Although not AD-specific, this illustrates the potential of ML to turn large HTS data repositories into predictive tools, dramatically enriching for actives.[102]Datasets for AD targets might be small or imbalanced comprising of far fewer actives than inactives, which complicates model training. Imbalanced data require special handling like oversampling, adjusted loss, etcin order to avoid trivial classifiers. In practice, every ML “hit” must be experimentally validated and must be subjected to molecular docking to confirm it’s true activity against the target of our interest.

4.8 Target Deconvolution

Target deconvolution is also called as target fishing, it is a pivotal process in phenotypic drug discovery, aiming to identify the molecular targets responsible for observed biological effects. [67]In classical drug discovery this step is slow and resource-intensive, often relying on chemoproteomics or knockout studies. However modern AI/ML approaches can rapidly narrow the search space. For predicting the target drug link knowledge garphs play a monumental role

4.8.1 Structure based Predictive Modelling

AI/ML models can directly predict drug–target interactions from chemical structure. Classic methods include similarity-based and QSAR models. For instance, unsupervised self-organizing maps (SOMs) are applied to predict the macromolecular targets of compounds like de novo drugs, natural compounds, anti-cancerous compound. Likewise, on chemogenomic fingerprints have been used to assign compounds to approximately 964 target classes in the WOMBAT (World Of Molecular BioAcTivity) chemogenomic database. [103]

Application of Random Forest classifiers are also one way to develop model for target fishing. The RF-QSAR target-fishing server uses RF models to rank candidate protein targets for a query compound. [104]Beyond these, kernel- and tree-based ML methods are also emloyed to predict binding affinities: e.g. KronRLS (regularized least squares on drug–target kernels) and SimBoost based on gradient boosting on drug/protein features obtained from known drug–target pairs. [105]Hybrid tools like BANDIT use Bayesian inference to combine drug efficacy data, transcriptomic profiles, chemical structures, side effects and bioassays, yielding high-confidence target rankings. [67]In sum, supervised ML on chemical and bioactivity features can generate ranked target lists for novel compounds.

4.8.2 Network Based Interference

Network models leverage biological and chemical interaction networks to infer targets from connectivity. Knowledge graphs (KGs) and PPI networks are employed to encode relationships between drugs, proteins,

pathways and the diseases associated with them. Graph-based AI can identifylikely drug–target edges and link prediction between them. For instance, in p53 (a tumour suppressor gene) activation pathway protein-protein knowledge graphs (PPIKGs) were constructed which ultimately integrated AI with molecular docking technique. By application of these graphs the researchers narrowed down 1088 protein targets to just 35 candidates. [106]More generally, **network pharmacology** integrates compound-target edges with disease gene networks in which targets that lie in network proximity to disease modules are prioritized. Network propagation algorithms (diffusing signals from known drug or disease genes through a PPI network) have shown strong performance in recovering true drug–disease associations. [107]Although examples in AD are still emerging, network-based ML has pinpointed key AD nodes. For instance, combined ML and network analysis of AD perturbation data recently highlighted **mTOR (regulated neuronal autophagy and survival) BCL2** (regulates apoptosis) as central hub proteins in the disease network suggesting them as indirect targets.[108]In practice, network ML approaches can uncover multi-target effects of drugs and suggest indirect targets in a disease network.

A deep convolutional neural network called AtomNet is designed for bioactivity prediction in structure-based drug discovery, leveraging 3D structural information of protein-ligand complexes. It is a DNN based model that is used in QSAR and in bioactivity prediction.

4.8.3 Omics Data Integration

Modern ML can also harness high-throughput omics (transcriptomics, proteomics, etc.) to deconvolute targets. A classic strategy is **signature matching**: comparing a compound's gene expression "footprint" to those of known perturbations. For example, the LINCS Connectivity Map (CMap) approach assigns a compound to targets by finding gene-knockdown or drug signatures that closely match the compound's signature. All known targets of similarly-acting perturbagens can then be proposed as targets. In practice, newer methods like graph convolutional networks incorporate this idea. A SSGCN model that embeds compound-induced and gene-knockdown expression profiles onto the PPI graph, then predicts interactions by correlating these embeddings was built. [109]In benchmarks on eight cell lines, this method (SSGCN) achieved 70–84% top-100 target accuracy, outperforming raw CMap and other approaches. Similarly, **ProTINA** is a network-based method that ranks targets by their influence on differential expression. Such *in silico* tools have shown significant gains in predicting true targets from expression data [109]

Xie *et al.* applied differential gene expression, weighted co-expression networks (WGCNA), single-cell RNA-seq and ML (LASSO, random forest, SVM-RFE) to analyse Alzheimer's datasets. This pipeline nominated "hub" AD genes (PLCB1, NDUFAB1, KRAS, ATP2A2, CALM3) as potential therapeutic targets. [110]They further identified drugs like noscapine and kinase inhibitors that act on these genes. In oncology, deep learning models have been trained on multi-omics (mRNA, mutations, proteomics, metabolomics) plus PPI graphs to predict drug responses, an approach that could be adapted to target deconvolution by linking omics profiles to drug effects. In summary, ML models that fuse omics data and networks can infer drug–target interactions and highlight disease-relevant targets from system-level data. [106]

In a different approach, **DRIAD**, an ML framework that trains on lists of genes differentially expressed in human neurons treated with drugs, correlating them with AD Braak stage was developed. DRIAD scored 80 FDA-approved or experimental drugs and found that JAK1/2 inhibitors (e.g. ruxolitinib rank among the top FDA approved hits) consistently produced signatures aligned with less severe AD pathology. [111]

AI/ML accelerates target deconvolution by leveraging large datasets. These methods can reveal hidden multi-target or pathway effects that are hard to detect by intuition alone. For instance, ML classifiers and network models outperform naïve similarity searches and can recover both known and novel targets more efficiently. By integrating diverse data (chemical, genomic, phenotypic), ML approaches can prioritize targets with higher accuracy and speed than purely experimental screens [106]They also enable rapid repurposing of compounds: for example, ML-driven repurposing screens in AD can nominate candidate drugs ready for preclinical testing, potentially saving years of early drug discovery work.

However, challenges remain. AI models depend on training data quality and coverage; gaps or biases in chemogenomic databases can lead to false positives or miss rare targets. If the model is trained on a biased dataset, with no hoolistic representation and lack of generalizability, these factors might lead to ineffective results. [105]Interpretability is also an issue: many ML predictions (especially deep nets) are "black boxes," making it hard to understand why a target was chosen. Finally, computational predictions must be experimentally validated, since ML cannot capture all biological complexity (e.g. context-specific protein expression, blood–brain barrier permeability in CNS).

4.9 De Novo Drug Design

In recent years, de novo drug design has undergone a paradigm shift, transitioning from conventional rule-based and experimental approaches to AI-driven generative models that offer improved scalability, chemical diversity, and predictive accuracy. Traditional methodologies, though foundational, often suffered from limitations such as complex synthesis routes and limited capacity to accurately predict the biological activities of novel compounds. [112]The first FDA-approved disease-modifying AD drug (lecanemab, 2023)[113] targets amyloid-β, but requires infusions and has safety limits. New targets (e.g. tau, neuroinflammation) and oral small-molecule or peptide drugs are urgently needed. [114]In contrast, AI-based de novo design can generate vast chemical libraries and simultaneously predict corresponding feasibility and pharmacological profiles across multiple optimization objectives. [115]The first step in de novo drug designing in generating novel compounds that have the same chemical, physical, structural properties as their SMILES, 3-D conformers, molecular graphic networks etc. [116]There are many additional AI models that have been implemented for de novo drug designing like Recurrent Neural Networks (RNNs). It is a deep neural network that aid in generating novel molecule by training on SMILES and predicting new SMILES that is based on the similarities between the input data and the novel molecule. LSTMs are especially employed in this procedure. [117] "Generative Adversarial Network" (GANs) is a ML model that is based on two distinguished networks called the generator that is fed with input data to train the model and another is Discriminator , that as it name suggest is used in spotting difference between the output novel molecule and the input SMILES. Hence by training both of thses network in an adversarial way, de novo drug synthesis can be accelerated.[118]

Latent space autoencoders like Variational autoencoders (VAEs) are ML models that is trained on dataset comprising of millions of drug obtained from online databases like ZINC, ChEMBL etc. Property-conditioned VAEs or predictor–decoder hybrids can generate new compouns with our desired property based on the SMILES fed into the model. Based on this working a cognitive molecular design model was created called PED: Predictor-Decoder-Encoder. It gathers similar compounds and ranks them for elimination of effective and non effective drug candidates [119], [120]

Another model which is based on PED is: RELATION. It is trained in such a way that it works generates drug molecules by extracting 3-D binding pocket interactions and structure in the respective protein ligand complex. It utilisesBiTL algorithm and Bayesian sampling to find inhibitors for two targets called AKT1 and CDK2 [114], [121]

Generative Adversarial Networks (GANs) develops Adversarial models (e.g. WGAN, MolGAN) to train a generator-discriminator pair to create realistic SMILES or graph representations. GANs have been applied to generate drug-like molecule design. Another approach, DeepTarget, developed by the Sakurai group, bypassed the structural data entirely by using only protein amino acid sequences to guide molecule generation, showing strong performance on DRD2 and PARP1 datasets.[122]

Policy-gradient or value-based Reinforcement Learning (RL) can optimize sequence or graph generators by rewarding desired properties like target affinity, drug likeness, cLogPetc. Early works used RL to bias RNNs toward dopamine receptor type 2 activity. In AD context, similar RL-guided fine-tuning can target AChE, BACE1, etc.[123]

Graph Neural Network (GNN) architectures generate molecules node-by-node or motif-by-motif. These directly model the chemical graph and can incorporate valence rules. For example, the masked graph model (MGM) iteratively builds molecular graphs and can control specified properties. [124]

Peptides and small proteins are increasingly considered as AD therapeutics (e.g. β-sheet breaker peptides, cell-penetrating neuroprotective peptides). The peptide space is vast (20^L sequences), so ML can greatly accelerate design. Deep generative models for peptides mirror those for small molecules: RNNs, VAEs, GANs and Transformer architectures have been applied to generate bioactive sequences.[125]Chaudhuri et al. described a Transformer-based generative model (“DeepTraPS”) for therapeutic peptides; such tools could be repurposed for AD targets.

In AD, computational peptide design has focused on inhibiting Aβ or tau aggregation. For instance, classical in silico screens identified novel β-sheet breaker peptides (e.g. PVFFE, PPFYE, PPFFE) that bind and destabilize Aβ42 fibrils. [126]Deep learning could automate and expand such efforts: a generative model conditioned on Aβ-binding motifs could propose hundreds of candidate peptides.

4.10 Virtual Screening

Virtual screening refers to the computational process of identifying bioactive chemical entities (hits) from curated databases or commercially available compound libraries. This strategy significantly enhances the efficiency of early drug discovery by prioritizing promising candidates and eliminating compounds that

do not effecientlyreat with the target and further rank them based on their score. [127]Traditional virtual screeningcomprises processes like molecular docking, pharmacophore modelling, which are often less accurate.

Virtual screening can be classified into two types, Structure based virtual screening (SBVS), docking candidate compounds into a 3D target structure and Ligand based virtual screening(LBVS), using molecular descriptors or fingerprints of known active compounds. [128]Classical ML models like Naïve Bayes, k-nearest neighbours, etc, have both been employed to accelerate VS. These models are trained on known actives/inactives to distinguish binders from non-binders and then used to screen large libraries for novel hits. ML-based VS pipelines often combine several steps: data curation (removing duplicates/decoys), feature generation, model training/validation, and then screening with post-filters (e.g. docking or ADMET prediction). Each model requires careful validation (cross-validation or held-out test sets) and performance evaluation by metrics like ROC–AUC, accuracy, precision/recall, F1-score or Matthew's correlation.[129], [130]

Classical ML models play a pivotal role in VS but recently these models have been overpowered by the deep learning models. Typical workflow in using classical ML model is firstly,a set of compounds is curated from databases and they are segregated based on actives or inactives for AD then the model is trained on these compounds, followed by addition of compute molecular descriptors or fingerprints like SMILES etc, after curating all the datasets and filtering out relevant compounds a classifier like Naïve Bayes, kNN, SVM, Random Forest is trained to predict activity. The model must be validated to improve the efficacy of the whole procedure, and then it is applied to screen new compounds. For example, **random forest (RF)** and **support vector machine (SVM)**is often used in QSAR modelling for AD targets.[131]

Deep learning provides more flexible representations with less manual feature design. Convolutional neural networks (CNNs) have been applied both in 3D structure-based scoring and in 2D image/graph-like formats. For example, CNN-based scoring functions (like AtomNet or GNINA) take 3D protein–ligand grids as input and automatically learn spatial features of binding. Deep learning scoring functions for instance, AtomNet, DeepVS, Ragoza's CNN, have matched or exceeded traditional docking scores. They prove to be more effecient than the traditional docking techniques by AutoDock[132]

Structure-based VS (SBVS) uses a target's 3D structure (e.g. Aβ oligomer models, BACE1 crystal structures) to dock and predict the binding pattern between drug and target and score the respective compounds. AI/ML complements SBVS by learning improved scoring functions or accelerating pose generation. For instance, ML scoring (RF-Score, NNScore) and CNN models (AtomNet, K_DEEP) have replaced empirical scoring, improving binding affinity prediction.[132], [133]DeepDocking pipelines use GNNs for ultra-fast affinity screening. Ligand-based VS (LBVS) relies on known ligands. AI/ML is used to perform similarity clustering and pharmacophore modeling of drugs.

STAGE	AI, ML MODEL	DESCRIPTION
Target Identification	PandaOmics	Deep learning or supervised based learning model[75]

Target Validation	GNN Based PPI prediction [87]	GCN, predicts PPI by 3 D modelling of structure[87]
Hit identification/ and virtual screening	AtomNet. DeepVS	CNNs, finds structurally similar compouns and runs them against the target[132]
Structure based predictive Modelling	WOMBAT[103], RFQSAR[104]	Random Forest algorithm utilized,Classifiers trained on SMILES[104][103]
De Novo Drug Design	RELATION	Predicts 3-D binding pocket interaction[121]
Drug Repurposing	NETTAG[134], DeepDR[135]	To identify AD associated risk gene by GWAS and multi-omics data[134]

Table 1 :List of AI, ML databases that assist in each step of drug discovery

5. AI, ML Resources for repurposing Anti Cancerous drugs for AD

Drug repurposing—also known as repositioning or reprofiling—entails investigating approved drugs for their potential to treat other medical conditions. A major advantage of this approach is that these drugs already have established safety and pharmacokinetic data, reducing the uncertainty in their development for new uses.This hastens the process of drug development and reduces cost factors. This repurposing is possible as many drugs are believed to have various targets and these drugs act upon different target to result in different phenotype or genotype modulation. AI, ML revolutionizes the field of drug discovery by integrating multi omics complex datasets with established extensive protein-protein network to identify new drug candidates and repurpose the old drugs.

AI models are employed in this repurposing in multiple ways, for instance one such integration is, identification of potential AD causing gene when mutated by application of Bayesian algorithm along with a network like system for gene and protein-protein interaction. After the shortlisting of the repurposed drug candidates, they are ranked according to their similarity score to the actual drug molecule. In final step the drug candidate can be analyzed by comparing with data obtained from various patients etc and testing it in in vitro condition. [136]

In some studies, deep-encoder-decoder models are used for first inferring and comparing the known link between the AD target genes, disease and the drug and then after obtaining the prioritized targets, novel chemical entities or repositionable drug candidates can be tested along those target genes. [65]Resources

like the Connectivity Map (CMap) and LINCS L1000 provide extensive drug-induced transcriptomic profiles that enable systematic drug repurposing.

Drug Gene Budger (DGB), Connectivity Map or CMap is a landmark database fordrug-induced gene-expression profiles and its successor LINCS L1000 are widely used. It is an online tool that containsa large collection of transcriptomics data, based on these several drug induced gene expressions, the drug molecules can be prioritized.[137]Similarly another online tool that incorporates CMap is Gene2Drug,[138]that utilizes the data obtained from CMap, and then analyses approximately 1300 drug signatures and multiple pathway annotations to link AD-associated gene sets obtained from GWAS or single-cell studies of multiple cell lines, to candidate drugs.[139]

One of the most unique ML framework models in the field of drug repurposing is DRIAD (Drug Repurposing in AD) ML framework, it ranks the differential gene expression due to treating of neural cells by almost 80 FDA approved drugs, top scoring drug emerges as the potential repositionable target candidates, whose expression profile correlated with AD Braak stage. This unbiased screening highlighted JAK inhibitors (baricitinib) and anticancer EGFR inhibitors (lapatinib, gefitinib) as top candidates against AD. Overall, CMap/LINCS-based pipelines can prioritize cancer drugs whose gene-expression signatures oppose AD pathology.[111]

5.1 Network based drug repurposing: -

Network-based approaches for drug repurposing construct protein–protein and disease–protein interaction maps to connect AD pathology to drug targets. For example, tools like STRING and STITCH integrate PPI and drug–target data to identify candidates, which can then be evaluated with platforms like CoDReS. STRING (string-db.org) which is a PPI database and **MIST** which provides data on genetic/protein interaction, supply drug–target neighbour information. By applying a database known as STITCH (http://stitch.embl.de/), these drug target interactions are evaluated. After obtaining these shortlisted drug candidates they are evaluated for their repurposing ability against AD targts. This is achieved by CoDReS tool (http://bioinformatics.cing.ac.cy/codres) [140]In a study conducted by Taubes et al. (2021), to conduct computational drug repurposing for Alzheimer's disease (AD), they applied a transcriptomics-based perturbation analysis of compounds targeting the APOE4 pathway. Their study demonstrated the therapeutic potential of **bumetanide**alters the APOE4 linked pathways, a key genetic risk factor in AD pathogenesis. Building on transcriptome-level insights.[141], [142]

A deep learning based model was constructed called DeepDR (Deep Drug Response). It substitutes for a graph neural network (GNN)-based architecture that integrates heterogeneous biomedical networks to generate high-dimensional embeddings of drugs and diseases, enabling accurate prediction of drug–disease associations.[135]

“DeepDrug”,is an AI driven drug repurposing model that built a heterogeneous biomedical graph and trained a graph neural network to select five-drug combos; one predicted combination included the cancer drug **niraparib** (PARP inhibitor) alongside others. DeepDrugrepresents operates by integrating knowledge about disease causing gene, genetic biomarkers, gene expression profiling, disease related molecular interactions etc, with its artificial intelligence (AI)-driven computational framework, thereby

addressing the limitations inherent in purely data-centric methodologies. A core innovation of "DeepDrug" lies in its construction of a heterogeneous biomedical knowledge graph, which encodes diverse biomedical entities (nodes) and their interrelations (edges) within a unified topology. Unlike conventional approaches that depend exclusively on data-driven learning, "DeepDrug" incorporates critical AD-related biological pathways and mechanisms, surpassing earlier AD-specific biomedical graphs by incorporating node and edge weights as well as directed edges with positive or negative semantic values (e.g., activation or inhibition). Such enhancements allow the framework to capture the functional directionality and relative strength of biological interactions, leading to a more expressive and biologically faithful representation of Alzheimer's-specific knowledge. To process and derive insights from this enriched graph, "DeepDrug" employs Graph Neural Networks (GNNs). This approach significantly departs from traditional network-based algorithms that are limited to simplistic metrics such as shortest path calculations. By leveraging domain-informed features, such as quantitative drug-target binding affinities and mechanistic annotations like activation or suppression, encoded through weighted and signed edges, "DeepDrug" enhances the fidelity of predictive modelling, thereby improving the prioritization of candidate compounds for repurposing in AD therapeutics.[143]

In another application of "DeepDrug" model has generated the list of top repurposed drugs that can be used in treatment of AD. Among these, **Tofacitinib**, an FDA-approved Janus kinase (JAK) inhibitor, emerged as the leading candidate and was subsequently successfully validated in preclinical trial on AD mouse models. Notably, three of the top five candidates out of the resulting 15 drug candidates, were JAK inhibitors, highlighting their role in mitigating neuroinflammatory processes, a central hallmark in AD pathophysiology. The remaining two top-ranking compounds, **Niraparib** and **Palbociclib**—both approved anticancer agents—were proposed as AD repurposing candidates through their effects on autophagy modulation.[144], [145]

Expanding this paradigm, Xu et al. (2022) proposed **NETTAG**, which leverages genome-wide association study (GWAS) signals and multi-omics datasets to identify AD-associated risk genes and prioritize therapeutic targets. This model incorporates a modified GNN capable of capturing topological sparsity and clustering within protein–protein interaction (PPI) networks. [134]

"An AI based Drug Discovery Network called AI DrugNet" was built for identifying novel drugs. Pan *et al.* (2023) developed a graph-based deep-learning framework for Alzheimer's drug repurposing. They first construct an Alzheimer's-specific network of drug–target pairs (DTPs) and define "drug-target quartets" which signifies two drugs and their targets as potential combination therapies.[146]This model is based on a graph convolution network that is trained on the data of interaction between drug-drug, drug-target as well as target targetDrugBank, disease specific synergistic information which is extracted from OptiCon and consequently forms a "DTP network", in which the nodes represent "drug-target pairs" and the edges symbolize associations between drug- target pairs. This uniquesystem is created and evaluated to identify drugs that can be used in combinational therapy as well as multi-drug therapy against AD as well as drug candidates that can be repurposed and modulated to cater to supress and down regulate AD targets, like anti cancerous drugs etc. In this a "deep learning-based model DeepDTQ" is constructed to analysed drug target interaction to identify drug combination therapy for treating AD.[146]

Rodriguez *et al.* (2021) describe “DRIAD (Drug Repurposing In AD)” as a machine-learning framework that correlates patterns of gene expression obtained from neuronal cells under effect of drug, with Alzheimer’s Braak stages.[111]It links drug-induced gene expression to AD severity; it ranked drugs like ”baricitinib” which is a JAK inhibitor and several EGFR-targeting cancer drugs like ”gefitinib, lapatinib” as top AD candidates.[149]

Advani *et al.* used genomics and proteomics networks to link AD risk genes with drug targets.[140] They firstly queried DrugBank/TTD for approved cancer drugs that interact with these AD-related proteins and identified dozens of candidates. For example, several VEGF/FGFR inhibitors emerged as candidates, though only those meeting blood–brain barrier criteria were kept. Notably, some of the retained drugs have reported neuroprotective activity: for instance, gefitinib and erlotinib have been shown to improve memory function in AD models, imatinib reduced amyloid-β accumulation, and ”vandetanib" inhibits acetylcholinesterase. [140]
In fact, Rodriguez *et al.* (2021) observed that their DRIAD pipeline ranked EGFR-targeting kinase inhibitors (like erlotinib) among the top repurposing candidates, aligning with the predictions of Advani *et al*. [147]

MODEL	AI/ML FRAMEWORK	LEARNING MODEL	DATA SOURCE	OUTPUT/ ANTI CANCER DRUG IDENTIFIED
Taubes et al., 2021 [141]	Transcriptomics-based Drug Perturbation	Differential Expression + Pathway Analysis	APOE4-related gene expression data	Identified Bumetanide (diuretic, anti-inflammatory potential)
Bayraktar et al., 2023 [148]	Gene Expression-Based Drug Repurposing	Expression Signature Matching	Gene expression datasets (glutaminase pathway)	Linked glutaminase inhibition to AD; repurposed drugs not named
Zeng et al., 2019 – DeepDR[144]	Biomedical Network Embedding	Graph Neural Network (GNN)	Drug-disease interaction networks	General repurposing model; foundational for later AD work
Xu et al., 2022 – NETTAG[134]	GWAS & Multi-Omics Integration	Modified Graph Neural Network (GNN)	GWAS + PPI networks + transcriptomic data	Prioritized AD-risk genes and druggable targets
Pan et al., 2023 – AI-DrugNet[146]	Drug–Target Pair Prediction	GNN-based Drug Combination Predictor	Drug–target pair networks	Predicted effective drug combinations for AD
Pan et al., 2024[143], [145]DeepDrug	Drug Combination Scoring & Prediction	Hybrid GNN + Scoring Function	Integrated from AI-DrugNet + biomedical features	Identified top drugs: Tofacitinib, Niraparib, Palbociclib

Table 2 : AI, ML models used in drug repurposing

6. Potential Therapeutic targets for drug repurposing in AD

Tyrosine Kinase Inhibitor (TKIs) are One of the most prominent inhibitors of tyrosine kinase is Nilotinib which was initially used for leukemia, has been used in NDDs like AD. It targets the root cause of the disease and combat symptoms AD by toxic clearance and enhancing autophagy. Hence it can be used as a potential candidate for drug repurposing. More broadly, targeting aberrant kinase signalling (including PI3K/Akt) might dampen both tumour growth and neuronal injury.

RXR Antagonist Bexarotene, an anticancer retinoid X receptor agonist, markedly reduced Aβ burden in AD mouse models and improved behaviour. In one study, bexarotene rapidly cleared brain plaques; a related chemotherapeutic, “carmustine” also lowered Aβ generation. These findings spurred interest in bexarotene’s neuroprotective potential, although human trials have been mixed. Nevertheless, “bexarotene” exemplifies how lipid/cholesterol pathways (via APOE modulation) can be targeted in both diseases. [22]

Microtubule Stabilizers likeTaxanes (e.g. “paclitaxel”) are cancer chemotherapies that stabilize microtubules. They have been proposed as AD treatments to counteract tau pathology. For example, taxanes rescued neuronal structure in AD models and hence are regarded as potential therapeutics for AD. Likewise, other anti-neoplastic drugs that affect tau phosphorylation or protein clearance for example, cerium oxide nanoparticles as antioxidants, are under investigation for AD.

Autophagy and Redox radicles are the main agents for triggering neuroinflammation in AD. In cancer, as well, the amount of ROS is found to be upregulated. Autophagy is another cellular mechanism that is dysregulated in both AD and cancer. However, this programmed cell death is reoccuring in the former one while in later it is turned off. Hence autophagy and redox Modulator like drugs are used to combat both. Agents that boost autophagy like rapamycin or antioxidant defences like NRF2 activators may benefit both conditions differently: enhancing neuronal survival in AD and disrupting cancer cell homeostasis. Tailored antioxidant or metabolic drugs are under study to rebalance ROS and protein turnover.[149]

Immunomodulation Strategies work by shifting the immune environment could have dual benefits. APOE-directed immunotherapies by mimetic peptides are being tested for AD and might also affect tumour immunity. Conversely, checkpoint inhibitors that mediates cancer immunotherapies are being evaluated for neuroinflammation control. In sum, insights into shared pathways are guiding novel interventions. Repurposing oncology drugs like “nilotinib”, “bexarotene”etc, offers one route as does targeting molecular hubs like p53 or PI3K/mTOR. Ultimately, understanding the molecular crosstalk between cancer and AD may yield treatments that tilt the balance toward cell survival in the brain without promoting malignancy or vice versa.

7. Promising Anti-Cancerous repositionable drugs for AD

The potential anti cancerous drugs that can be repositioned target both AD and Cancer can be classified in 5 ways. The most prevalent and efficient one being **tyrosine kinase inhibitor (TKIs)**. These are used for targeted therapy in cancer by blocking the activity of altered tyrosine kinase (essential for cell signalling and growth) activity in cancer cells, hence preventing them from proliferating. These small molecules of drug act as competitively inhibit ATP and prevent binding of ATP to tyrosine kinase enzyme. This blocks the cascade of down streaming pathway responsible for cell growth, survival and proliferation. These drugs combat NDDs by promoting amyloid clearance and reducing neuroinflammation and tau phosphorylation. Five TKIs are currently being tested in laboratories for AD. “Nilotinib”, reduces amyloid plaque deposition and reduces inflammation. “Dasatinib” eradicates senescent cells from the neighbouring microenvironment of amyloid plaques and inhibits amyloid-dependent microgliosis. Tyrosine-kinase inhibitor (TKI) are one of the major classes of repositionable drugs or AD. TKIs like “Bosutinib” is used to treat chronic leukemia. The mechanism underlying this drug is that it eradicated toxic amyloid plaques, reduce neuroinflammation, by inhibiting non receptor tyrosine kinase, AbI, and hence modulate the immune system of the central nervous system. These findings suggest that TKIs, particularly bosutinib, could be effective in treating early-stage Alzheimer's disease. [150], [151]
Immunomodulatory Agents likeLenalidomide and thalidomide are being explored for their potential effect in cancer and NDDs, as they harbour the potential to either activate or supress the immune system. These agents can reduce pro-inflammatory cytokines, which are implicated in AD pathology. Another promising candidate is “Dasatinib”,it is an immunosuppressive agent. The application of this drug is usually in combination with quercetin as a senolytic therapy. This combination has successfully entered the clinical trials for treating symptoms of AD patients. The joint action of these two drugs can reduce the overproduction of cytokines as that might cause inflammation and alleviate cognitive disorder symptoms in AD mouse models by selectively removing senescent oligodendrocyte progenitor cells. Another popular class of anti-cancer drugs that can be repurposed are Retinoid X Receptor (RXR) Agonists. These are nuclear receptors that plays various roles in cell processes like cell growth, differentiation, apoptosis etc.Bexarotene and tamibarotene, which are RXR agonists, are under investigation. Bexarotene enhances Aβ clearance and reduces neuroinflammation in preclinical studies, though it has shown limited central nervous system (CNS) penetration in human trials.[23]
Monoclonal Antibody likeDaratumumab, is being used to attenuate AD pathology. It targets cells exponentially expressing CD38 and promote their apoptosis in cancer. It’s mechanism is also relevant in neurodegeneration and neuroinflammation in many NDDs including AD.
Drugs that alter the histone acetylase activity by targeting histone deacetylases (HDACs) enzyme that regulates gene expression by removing acetyl group from the histones around which DNA is wrapped are called Histone Deacetylase (HDAC) Inhibitor. For example, Vorinostat, an HDAC inhibitor, has the potential to restore synaptic plasticity and improve memory in NDD patients indicated by long term potentiation. HDACI have antiproliferative effect in cancer cells while amyloid clearance and reduction in tau pathology in AD. [152], [153]
One of the most promising FDA approved drug that was repositioned is Tamoxifen, which is an oestrogen receptor modulator in breast cancer caused by hormonal imbalance. It acts by inhibiting the driving genes responsible for the apoptotic cell death pathway and hence said to have neuroprotective

function as well. A study conducted on these results further confirmed these findings by noting that prolonged use of “tamoxifen” resulted in sparse chance of developing dementia in patients. [65]

8. Bridging the gap: Translating AI/ML advances into clinical realities: Challanges and Opportunity

As the NDD cases in the nation increase at an alarming rate, there is an urgent need to combat these disorders with a novel and unique approach.

Drug repurposing emerges as a boon in present time. Repurposing already well known anti cancerous drugs whose pharmacokinetic and toxicological properties are known and reprofile them based on their likelihood to bind to the desirable target to develop a drug against AD. The incorporation of AI/ML in this repurposing provides a futuristicapproach to develop novel drug candidates as well as repurpose already known drug to hasten the process of drug development and reduce the costly procedures.

The biggest challenge in incorporation of AI, ML in biomedical field is translating the findings to clinical settings. Although AI/ML models often exhibit high performance on training datasets but may fail to generalize to diverse clinical populations. This discrepancy arises due to differences in data distributions between research settings and real-world clinical environments. Ensuring that models are robust across various patient demographics and clinical settings is crucial for their successful implementation. Failure in interpreting AI, ML datasets handicap the purpose of their incorporation into clinical predictions. In another words, these deep learning models act like a black box, that creates a hurdle for general clinicians and practitioners to understand the generated results. This creates a lack of transparency and trust and a reluctance to their integration into medical data to transform the field. This remains the biggest challenge till date. Another challenge that might be faced is the incorporation of heterogenous datasets from different sources and format to AL/ML algorithms. For optimum results and minimum discrepancy in data analysis, the data needs to be standardized. Standardized and High data quality are the key to avoid sub-par results.

Apart from these struggles there are many data gaps and biases in AI,MLresearches like underrepresentation of diverse population. Datasets used to train AI models often lack diversity, leading to biases that can adversely affect underrepresented groups. For instance, models trained predominantly on data from specific ethnicities may not perform well on others, exacerbating health disparities. [154] Hence there is a pressing need to develop an inclusive approach to address these biases and extract high quality data from these models. This opens a floodgate of opportunity to develop personalised medicine and provideequitable opportunity to everyone without discrimination. Another challenge using thesse models is bias in data collection and labelling. While sourcing the data and labelling it, certain group of individuals might be overlooked creating a biased data. The biggest disadvantage of this biasness is that it leads to skewed datasets that affect the model’s performance and impairs the ability of the model to produce diverse and holistic results. Recognizing and mitigating these biases is critical for developing fair and effective AI systems. There are many Regulatory and Ethical Considerations also associated with this, like breach privacy and data security. The usage of health data of patients and their medical history might be considered invasive by many folks. Ensuring compliance with regulations like HIPAA and GDPR is

essential to protect patient information. The results extracted from AI models might fail at the multilevel clinical trials, therefore to overcome such errors, thorough and meticulous validation of these drugs need to be done before putting these compounds through expensive clinical trials.

In case of adverse outcomes placing responsibility and accountability becomes difficult while dealing with AI, ML models. Clear guidelines are needed to delineate accountability among developers, clinicians, and healthcare institutions, for ethical use of AI. Ethical considerations, including informed consent, transparency, and the potential for algorithmic bias, must be addressed to patients before using their data to ensure that AI applications align with societal values and do not inadvertently cause harm.

9. Conclusion

The convergence of oncology and neurodegeneration has opened a promising frontier in the search for therapies for Alzheimer's disease (AD). AD and cancer – 2 prominent diseases in today's world, overlap due to the dysregulation of fundamental cellular processes, like cell cycle regulation, cellular proliferation, etc. This overlap is exploited by researchers in order to repurpose anticancer drugs for AD. This proves to be a highly strategic and cost-effective therapeutic avenue. Many anticancer agents target pathways such as cell cycle regulation, autophagy, stress caused by generation of ROS , and mitochondrial function, all of which are also implied in the pathophysiology of AD. Drugs such as **Palbociclib**, Tomoxifan, Dastainib, **Niraparib**, and **Tofacitinib**, etc originally developed for treating malignancies, have demonstrated potential neuroprotective function in AD models. Kinase Inhibitor, alkylating agents, antibodies etc are the major categories of drug that are being repurposed to reduce neuroinflammation and ultimately combat neurodegeneration in AD. With the advancement of computational frameworks, AI, ML and many other deep learning models have proved to be a saviour in hastening the drug developement process. Hence with the passage of time the drug discovery pipeline is shifting towards incorporation of these models to either develope novel drug candidates or repurpose the already approved drug by levaraging their safety profile, to combat many diseases like AD in this case. Thses advanced computational models achieve this by employing a range of different algorithms like graph neural networks (GNNs), deep auto encoder-based framework to deep reinforcement learning (DRL). These models have facilitated every step of the drug discovery process along with the efficient high throughput screening of vast online repositories and then finding the synergistic relation drug target relationships by these graph networks and shortlisting them etc. AI-driven platforms such as DeepDrug, AI-DrugNet, and DeepDR have not only expedited the discovery process but also enhanced accuracy, scalability, and reproducibility. These models have helped in finding the putative disease-causing targets and repurposing potential drugs against these targets. These tools are instrumental in deciphering complex omics datasets, predicting molecular targets, and tailoring personalized treatment strategies for multifactorial diseases like AD. Yet, the path forward is not laden without challenges. Transforming these computational findings into clinical drug trials requires leveraging the strengths of both biomedical sciences and computational intelligence. There are many ethical constraints associated with the use of AI, ML in biomedical field. Therefore, considerable measures need to be followed for thr incorporation of these models into datasets. As we stand at the crossroads of two major medical challenges—cancer and Alzheimer's—the fusion of drug repurposing strategies with AI/ML presents a unique approach to combat two problems with one cumulative solution. Researchers must break down disciplinary silos to

foster collaborative innovation, leveraging the strengths of both biomedical sciences and computational intelligence. Investment in high-quality, diverse datasets; transparent AI models; and supportive regulatory frameworks will be key to translating these technological advances into tangible health outcomes. AI platforms play a monumental role in inventing individualized drug therapy and in precision medicine that caters to a particular patient, in case of auto-immune or other complex disorders. This is done to improve the therapeutic efficacy of the treatment given and finely tailor the treatment according to the progression of the disease.

In conclusion, the strategic repurposing of anticancer drugs for Alzheimer's disease, empowered by AI and ML, is more than a hopeful possibility—it is a revolution in the field of biology. By embracing this interdisciplinary synergy, we can accelerate the development of effective treatments and bring renewed hope to millions affected by neurodegenerative disorders. The time to act is now, at the intersection of biology and data lies the future of medicine.

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- Phylogenetic Tree Construction
- DNA Sequencing

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- Analayze proteins Structure

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