Emerging Therapies of Alzheimer's Disease: A Comprehensive Review

By

Md Abtahi Tasin

18346023

A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy (Hons)

School of Pharmacy

BRAC University

November 2022

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I/we have acknowledged all main sources of help.

Student's Full Name and Signature

Md Abtahi Tasin

ID: 18346023

Approval

The thesis titled “Emerging Therapies of Alzheimer’s Disease” submitted by Md. Abtahi Tasin (18346023), of Spring 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on October 2022.

Supervised By:

Kazi Fatema Rahman
Lecturer, School of Pharmacy
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study does not involve any kind of animal and human trial.

Abstract

Alzheimer's disease is a complex, debilitating neurodegenerative disorder, with a rapidly increasing worldwide prevalence. Despite decades of intense research, therapeutics for Alzheimer's disease are still limited to symptomatic treatments that provide only short-term relief. In recent years, a range of new therapies with better precision have emerged; some are at the pre-clinical stage while some have been tested in clinical trials too. The aim of newer therapies it to treat the underlying cause of AD, provide more safety and long term efficacy. Besides, innovative strategies such as artificial intelligence and personalized medicine have also been introduced to provide more targeted treatment based on patient characteristics and genetic makeup. This comprehensive paper will discuss the various emerging therapies for AD including small molecule drugs, gene therapy, stem cell therapy, followed by a glimpse into the knowledge gaps that will guide research into AD therapeutics over the next decade.

Keywords: Alzheimer's Disease, Cognitive dysfunction, Artificial intelligence, Gene therapy, Stem cell therapy, Small molecule drugs.

Dedication

It is dedicated to my respected supervisor Kazi Fatema Rahman Mam and my parents for constantly supporting me through this tough time. I also want to dedicate this to all the patients who is suffering from Alzheimer's disease.

Acknowledgement

First of all, I want to give thanks and appreciation to God, the Almighty ALLAH, for granting me good health as well as the patience, dedication, and knowledge I needed to finish the thesis.

To my project supervisor, Kazi Fatema Rahman, Lecturer, School of Pharmacy, BRAC University, I would like to convey my profound gratitude for all of her help and support throughout my research. Working under her direction was a great honor and privilege.

My sincere gratitude also goes out to Dr. Eva Rahman Kabir, Professor and Dean, School of Pharmacy, BRAC University for all that she does for the department and the students.

Lastly, I would like to thank my parents for always motivating me to stretch beyond my comfort zone. Additionally, I would like to thank everyone who has helped me whenever I have required it.

Table of Contents

List of Tables

List of Figures

List of Acronyms

AD = Alzheimer's Disease

CRP= C-reactive Protein

ROS = Reactive Oxygen Species

FDA= Food and Drug Administration

MAO= Monoamine Oxidase Inhibitor

DNA= Deoxyribonucleic Acid

Aβ= Amyloid Beta

IV= Intravenous

NGF= Nerve Growth Factor

iPSC= Induced Pluripotent Stem Cell

APP= Amyloid Precursor Protein

NFTs= Neurofibrillary Tangles

CNS= Central Nervous System

MSCs= Mesenchymal Stem Cell Therapy

PET= Position Emission Tomography

NMDA= N-methyl-D-aspartate

ChE= Cholinesterase Inhibitor

OLGs= Oligoden- Drocytes

Ach= Acetylcholine

ESCs= Embryonic Stem Cell Therapy

AI= Artificial Intelligence

ADDL= Aβ Derived Diffusible Ligands

GIP= Glucose-dependent Insulin-tropic Polypeptide

cAMP= Cyclic Adenosine Mono-phosphate

VDCC= Voltage Dependent Calcium Channel

GLP-1= Glucose-Like Peptide 1

IgG= Immunoglobulin G

ARB= Angiotensin Receptor Blocker

CCB= Calcium Channel Blocker

LDL= Low Density Lipoprotein

HDL= High Density Lipoprotein

GWAS= Genome Wide Association Studies

SMD= Standardized Mean Difference

CI= Confidence Intervals

Emerging Therapies Of Alzheimer's Disease

CHAPTER 1

INTRODUCTION

Alzheimer disease is a disorder that is a progressive neurodegenerative complex .In recent years, astonishing progress have been achieved in understanding both the genetic factors and molecular biology underlying the disease(Qiu et al., 2022a).The hallmark symptoms of Alzheimer's disease include beta amyloid plaques which are aggregates of misfolded proteins that form in the spaces between nerve cells and tau tangles(Chapleau et al., 2022)Alzheimer's is more likely to happen to women than to men. Alzheimer is known to be an age-related disease. In terms of global population 0.7% of women and 0.6% of men between 65-69 years suffer from the disease, and the prevalence goes up to 14.2% for women and 8.8% for men aged between 85-89 years(Mielke, n.d.)The estimated global prevalence of Alzheimer's disease is as high as 25 million, and it is expected to grow every 20 years until 2040(Qiu et al., 2022b.)The risk of Alzheimer's disease will continue to increase among the old people as their population will also increase (Mayeux & Stern, 2012).The United States Census Bureau estimates that by 2060, the prevalence of Alzheimer's disease will have increased from its 2014 rate of 1.6% to 3.3%(Patwardhan & Belemkar, 2021).Alzheimer's disease can occur due to various reasons .Alzheimer's disease risk appears to be increased by a number of heart and artery diseases. Cardiovascular disease may lead to Alzheimer's disease(Kocahan & Doğan, 2017).According to observational studies, having high blood pressure in middle age, particularly uncontrolled midlife high blood pressure increases the probability of developing Alzheimer's disease in later life. Heavy alcohol intake can lead to Alzheimer's disease(Abbas Tahami Monfared Michael Byrnes Leigh Ann White Quanwu Zhang et al., n.d.).Recent years have seen the introduction of numerous treatments for Alzheimer's disease. Current strategies to develop Alzheimer's disease treatments have not been fruitful. They may not be targeting the secondary effects that occur in the brain following the formation of amyloid beta plaques. The target almost commonly focused on for AD drug development has been amyloid beta plaques and their subsequent

elimination(Mehta et al., n.d.).There are no disease-modifying medicines that can stop or decrease the progression of the disease. The unmet clinical need is the usage of innovative drugs(Theleritis et al., 2019). Amyloid-β Pathology is regarded as a classic neuropathological feature of AD-affected brains which can lead to synaptic and neuronal loss(Ashford et al., 2021).Tau tangles are widely expressed microtubule-associated proteins in the brain that are linked to tubulin to enhance microtubule assembly(Pardo-Moreno et al., 2022).Regulatory load, risk-averse trial designs, lack of urgency, and not accounting for the consequences of inaction are obstacles to AD treatment development, leading to delayed clinical trials and higher overall expenditures(Dokholyan et al., 2022).For the treatment of Alzheimer's disease, a variety of medications are administered. Globally, Aducanumab, Tacrine, Rivastigmine, and Donepezil are used to treat Alzheimer's disease. Aducanumab is part of a new generation of monoclonal anti-Aβ antibodies that specifies and targets Aβ aggregates(Vaz et al., 2022).Donepezil is a cholinergic drug that blocks the action of acetyl-cholinesterase, the enzyme responsible for the breakdown of acetylcholine. Rivastigmine was introduced in Switzerland in 1997 and approved by the FDA in 2000 is used for the treatment of mild and moderate AD(Pardo-Moreno et al., 2022).Current AD treatments are symptomatic and do not cease or stop disease development. Conventional practices focus on investigating the neuro-protective efficacy of disease-modifying medicines in pre-symptomatic AD with bio-markers that predict disease progression(Corbett, Smith, et al., 2012).

Aim and Objective

- To discuss about emerging therapies of Alzheimer’s disease
- Comparative analysis between current and previous therapies of Alzheimer’s disease.
- Potential strategies to improve current therapies to provide better treatment for Alzheimer’s disease.

CHAPTER 2

Pathogenesis of Alzheimer’s disease

Neuronal death and synaptic atrophy are hallmarks of Alzheimer's disease, along with the formation of extracellular amyloid-beta plaques and neurofibrillary tangles within the cytoplasm. All these factors lead to a gradual decline in cognitive abilities. When tau is phosphorylated in an abnormal way, it may help to make neurofibrillary structures that are also abnormal.AD affects the reticular formation, the brain stem nuclei (thalamus, hypothalamus, locus ceruleus, amygdala, substantianigra, striatum, and claustrum), and the striatum. Excitotoxicity happens when NMDA receptors are constantly turned on. At different stages of Alzheimer's disease, premature synaptotoxicity, changes in how neurotransmitters are expressed, loss of neurophils, buildup of amyloid -protein deposits (amyloid/senile plaques), and loss of neurons and brain atrophy are all linked. Studies have examined how Amyloid Beta and NMDA receptors interact together. Aβ induced spine loss is associated with a loss in glutamate receptors and is dependent on calcineurin, which has been linked to depression(Kocahan & Doğan, 2017). Pathophysiology of Alzheimer’s disease is shown on Figure 1.

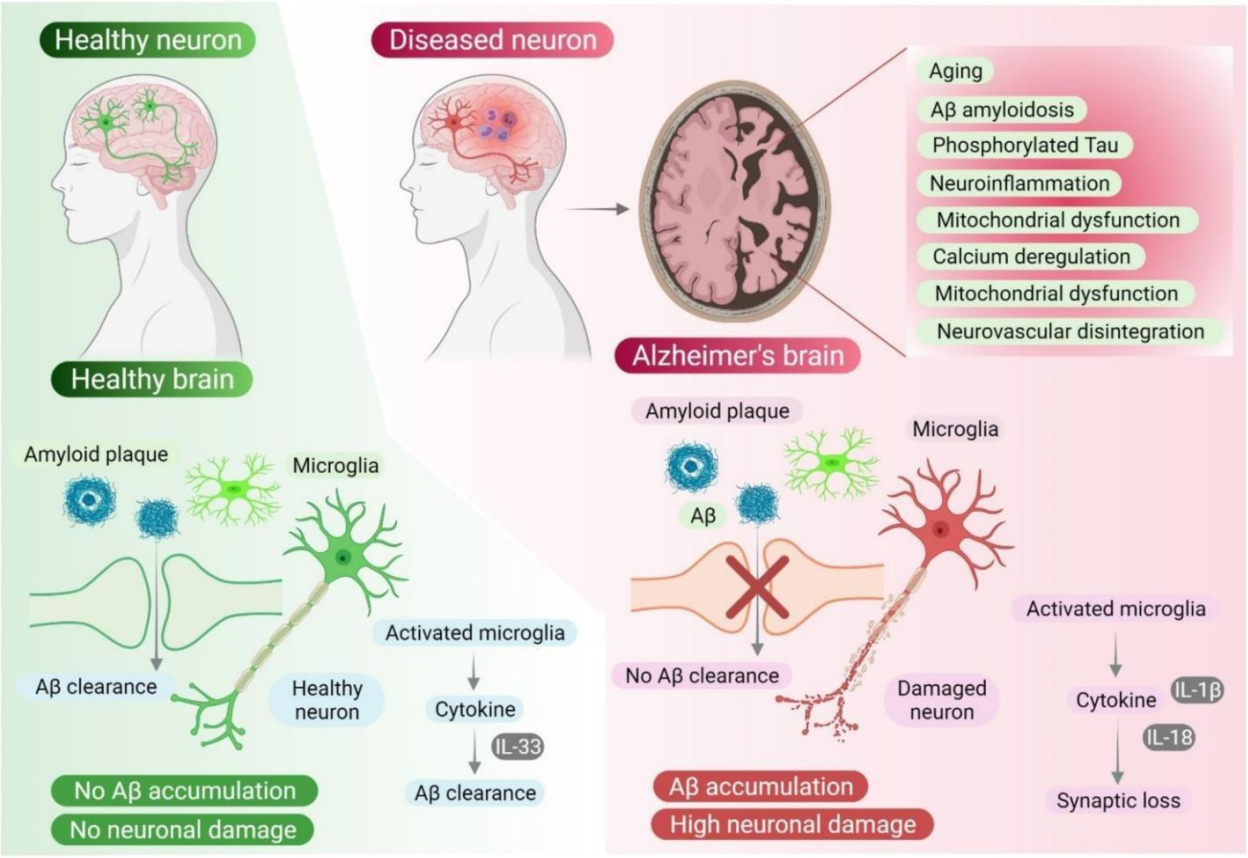


Figure 1: Pathophysiology of Alzheimer's Disease(J. Wang et al., 2013).

Various types of pathogenesis for Alzheimer's disease is briefly described.

Protein Misfolding and Aggregation

Alzheimer's disease is characterized by amyloid plaques and neurofibrillary tangles (NFTs), which are generated by misfolded amyloid-β peptide and tau protein (Trifunovic et al., 2022). Aggregates of misfolded proteins can accumulate intracellularly or extracellularly. Aggresomes are microtubule-dependent cytoplasmatic inclusion bodies that are generated when a cell's ability to destroy misfolded proteins is exceeded. Aggresomes typically contain cytoplasmic aggregates. The development of aggresomes may aid in the recruitment of protein aggregates destined for removal through macro-autophagy and breakdown in lysosomes(Moreno-Gonzalez & Soto, 2011).

Mitochondrial Dysfunction and Oxidative Stress

Decreased levels of ATP in neurons, which are indicative of mitochondrial dysfunction in AD, are linked to increased formation of reactive oxygen species (ROS). Brain cells like neurons and glia have high energy requirements. As a result the brain uses a lot of ATP to perform its operations. Reactive oxygen species are metabolic byproducts that can be both beneficial and harmful to a living system, making them a major contributor to oxidative stress(Misrani et al., 2021). Mitochondria are cellular organelles responsible for producing energy. They are also involved in a wide variety of neuronal processes, including calcium homeostasis, membrane excitability modulation, neurotransmission, and plasticity(Trifunovic et al., 2022).

Synaptic Dysfunction and Neurotransmitter Balance

Synaptic dysfunction in CNS diseases is caused by changes in synapse structure and function and can lead to certain pathologies. Active synapses are needed for neurotransmission, synaptic, and cognitive function. In AD and neurological illnesses, synaptic dysfunction and inadequate pre-post synaptic activity can lead to synaptic and neuron loss (Taoufik et al., 2018).Synaptic disruption plays a key role in AD pathogenesis, thereby maintaining a healthy neurotransmitter balance is critical. EDR peptide can protect hippocampal neurons from amyloid synaptotoxicity by enhancing dendritic spines(Trifunovic et al., 2022).

Destruction of the Blood–Brain Barrier and Dysfunction of the Vascular System

There is considerable evidence that the BBB is linked to neuro-degeneration, vascular damage, and inflammatory processes in Alzheimer's disease. Brain shrinkage, gliosis, and white matter degeneration are all symptoms of these shifts in the brain (Kurz et al., 2022). Classical AD

pathology, such as amyloid- plaques and neurofibrillary tangles, has been linked to vascular dysfunction. Vascular cells may release neurotoxic substances, modify the local inflammatory environment, and contribute to pathological remodeling of neuronal and glial networks (Govindpani et al., 2020). As a result of vascular malfunction and breakdown, neurotoxic plasma components, erythrocytes, leukocytes, and infections can enter the central nervous system. Early Alzheimer's disease patients have been found to have blood brain barrier abnormalities, specifically in the hippocampus and other gray and white matter regions (Trifunovic et al., 2022).

2.2 Sign and Symptoms of Alzheimer's disease

Loss of memories occurs as a primary symptom. Memory loss can manifest in a number of ways, including the recurrence of questions or discussions, the misplacing of items, the failure to keep appointments, and general disorientation .Lack of understanding about safety and risks are part of cognitive deficits. They face trouble managing money, making decisions, and completing multi-step activities like getting dressed. Some patients lack ability to remember a certain person. They also may exhibit lack of capability to use basic tools, difficulty balancing, finding it difficult to get dressed. Peoples with AD have a tendency of getting upset, angry, or worried more often than normal person(Joe &Ringman, 2019). Moreover it could affect their ability to evaluate distance, color, and contrast. Some other common side effects of Alzheimer's disease include a loss of appetite and difficulty communicating. However some patients may exhibit seizures, skin infections, difficulty swallowing, increased sleeping, hallucination and paranoia(Giovannetti et al., n.d.).The main signs and symptoms of AD have been shown in Figure 2.

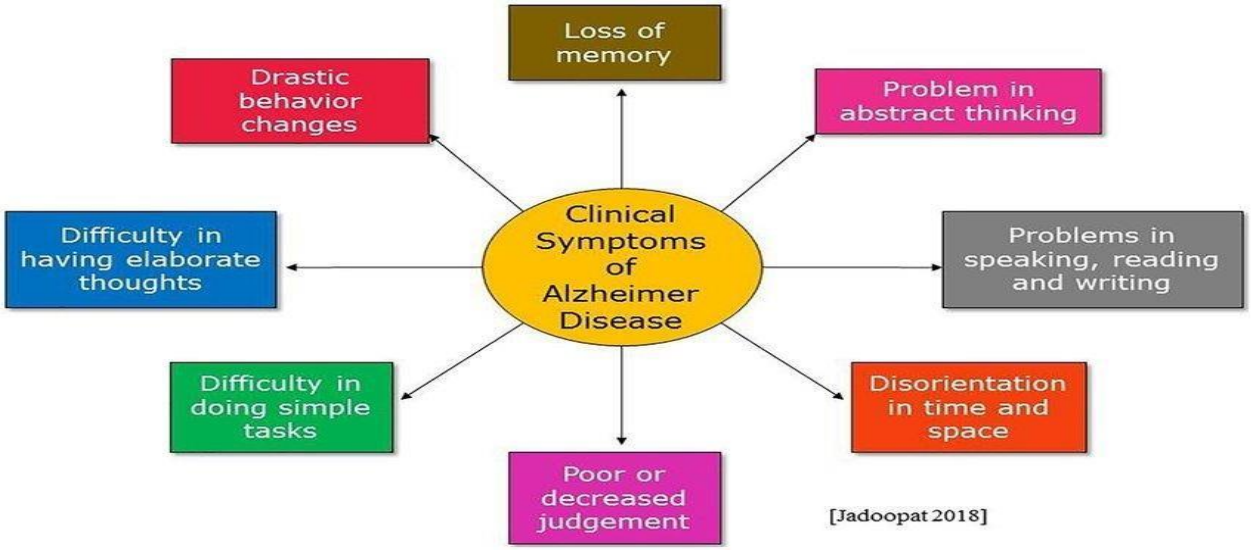


Figure 2: Symptoms of Alzheimer's disease (Bature et al., 2017).

CHAPTER 3

Pathology of Alzheimer’s disease

Alzheimer's disease is characterized by amyloid-beta plaques, neurofibrillary tangles, neuronal death, and synapse loss(Kocahan&Doğan, 2017).Difficulty in treating AD can be connected to the disease's complex multifactoral pathogenesis. Defects in cholinergic neurotransmission, beta-amyloid protein metabolism (Aβ aggregation), tau protein deposition and phosphorylation (NFT), Synapse pathology, FMNL2 regulated pathology, and the involvement of inflammatory and oxidative pathways all play a role in the pathogenesis of Alzheimer's disease(Athar et al., 2021).

Alzheimer’s disease and its pathogenesis is illustrated on Figure 3.

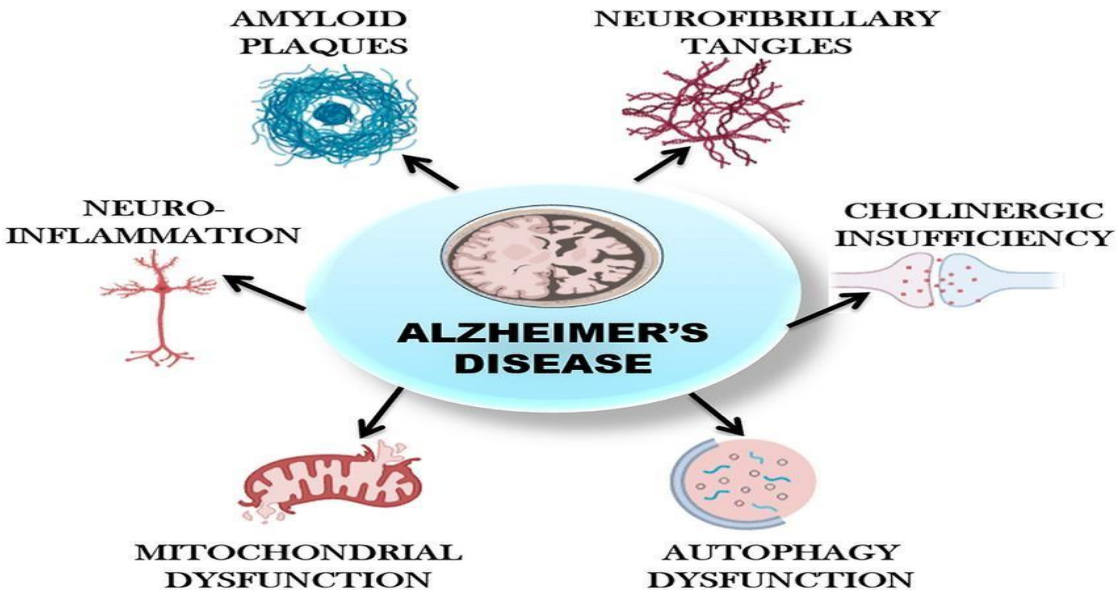


Figure3: Alzheimer’s disease and its Pathogenesis (Fan et al., 2020).

Synapse Pathology

Synapse loss and dysfunction are major features of Alzheimer's disease. Late-stage AD causes substantial neuron and synaptic loss(C. A. Briggs et al., 2017). Tau species has the ability facilitate synaptic impairments in Alzheimer's disease by interacting with certain synaptic proteins and mitochondria. It causes synaptic protein alterations and oxidative stress. They also cause persistent inflammation and glial cell over-activation, resulting to excessive synapse loss(Griffiths & Grant, 2022).

Tau indicated Pathology

There is a substantial relationship between tau pathology and cognitive decline in Alzheimer's disease brains. In Alzheimer's disease, aberrant tau proteins can be transmitted via specific neuro anatomical channels in the brain(Ando et al., 2021). Tau hyperphosphorylation seems to precede accumulation in AD neurons. Hyperphosphorylated tau was identified in AD neurofibrillary tangles and cytoplasm(Iqbal et al., 2005). The p-tau biomarkers in cerebrospinal fluid were accurate predictors of cognitive decline. Cerebrospinal fluid (CSF) p-tau231 has been frequently recognized as a biomarker for various stages of Alzheimer's disease (Ashton et al., 2022).

FMNL2 regulated pathology of Alzheimer Disease

FMNL2 expression was linked with amyloid and phosphorylated tau deposition in brain infarcts of AD patients. FMNL2 was very much crucial in cerebrovascular astroglia in AD(Lee et al., 2022).Formin is encoded by FMNL2. Formins govern actin and microtubules, affecting cell shape, cytoskeletal architecture, and cell–cell contact involved in Alzheimer's disease. FMNL2 is elevated in Alzheimer's disease astroglial cells, according to single cell transcriptomics. Detached gliovascular contacts can trigger inflammatory cells infiltration to the brains from the blood, aiding in amyloid elimination (Lee et al., 2022)

Monomeric C-reactive protein for Alzheimer's disease pathology

Increased circulating levels of C-reactive protein (CRP), a pentraxin produced primarily by the liver, are significantly connected with the pathogenesis of Alzheimer's disease. Furthermore, afflicted brain areas, including neurons, have been found to synthesize CRP. CRP comes in two different forms. Plasma concentration of native CRP are within the normal range when they are created during the acute phase of an inflammatory illness (Slevin et al., 2015). In the primary neurons, monomeric CRP increases the formation of amyloid beta and stimulates the phosphorylation of tau in addition to their associated proteins. C-reactive protein (CRP) is a protein made in the liver that increases substantially in the blood after hours of just about trauma or disease which induces tissue damage. It can be said mCRP is a crucial mediator in the APOE-related pathway of Alzheimer's disease risk (Gan et al., 2022).

CHAPTER 4

Small Molecule Drugs For Alzheimer’s disease

Drug Therapies for Alzheimer’s disease

Various types of drugs are used for treatment of Alzheimer’s disease. A number of medicines are available that can be prescribed for Alzheimer's disease that can ensure temporary improvement of some symptoms. Among those drugs the small molecule drugs are also included. Some small molecule drugs are Rivarstigmine, Galantamine, Donepezil which are Cholinesterase inhibitor. Moreover Monoamine Oxidase Inhibitor drugs like Selegiline and TV 3326 are also being utilized to treat patients with Alzheimer’s disease.

Small Molecule Inhibitors Of ADDL

ADDLs are Aβ derived diffusible ligands. It is highly represented in AD brain, where they bind to hippocampus neurons to cause cognitive impairment in rodents. Accumulating evidence now suggests that Aβ derived diffusible ligands (ADDLs) has a crucial part to play in the pathogenesis of AD(Shughrue et al., 2010).Fibril development and ADDL formation follow separate pathways. Certain tiny compounds that were initially designed to inhibit amyloid fibril formation have been hypothesized to also inhibit oligomer assembly. Alzhemed (3-amino-1-propanesulfonic acid), a small molecule mimic of sulfated glycosaminoglycans (GAG), is now undergoing phase III clinical trial and is a notable example. Plaque reduction in a transgenic Alzheimer's disease mice model was shown to be attributable to Alzhemed's potential Aβ monomer binding capability. According to the results from recently concluded 20-month open-label extension of a phase II trial, some individuals with moderate AD saw a slower rate of cognitive loss. But during the study's blinded phase, no beneficial effects were noted. There is evidence from a dot-blot assay showing that amine-, carbonyl-, and nitro-substituted phenols can inhibit Aβ aggregation. Curcumin, another substituted phenol, has been observed to disrupt Aβ assembly(Look et al., 2007).

Cholinesterase (ChE) Inhibitors

For the treatment of Alzheimer's disease cholinesterase inhibitors are being used. Donepezil and galantamine are selective inhibitors of acetylcholinesterase (AChE), although rivastigmine is a dual inhibitor of AChE and butyrylcholinesterase (BuChE).ChE inhibitors vary in terms of selectivity for AChE and BuChE, as well as pharmacokinetic and pharmacodynamic features, and these variations may have profound effects on safety, tolerance, and efficacy. According to the cholinergic hypothesis, acetylcholine deficiency contributes to the cognitive deterioration observed in Alzheimer's disease. The enzymes responsible for degrading acetylcholine (ACh) are inhibited by cholinesterase (ChE) inhibitors, leading to an increase in the amount of Ach

available that can trigger both nicotinic and muscarinic receptors in the brain. ChE inhibitors have been the standard method for treating AD symptoms ever since their introduction to clinical practice(Grossberg, 2003). The pathway of cholinesterase inhibitors is illustrated on Figure 4.

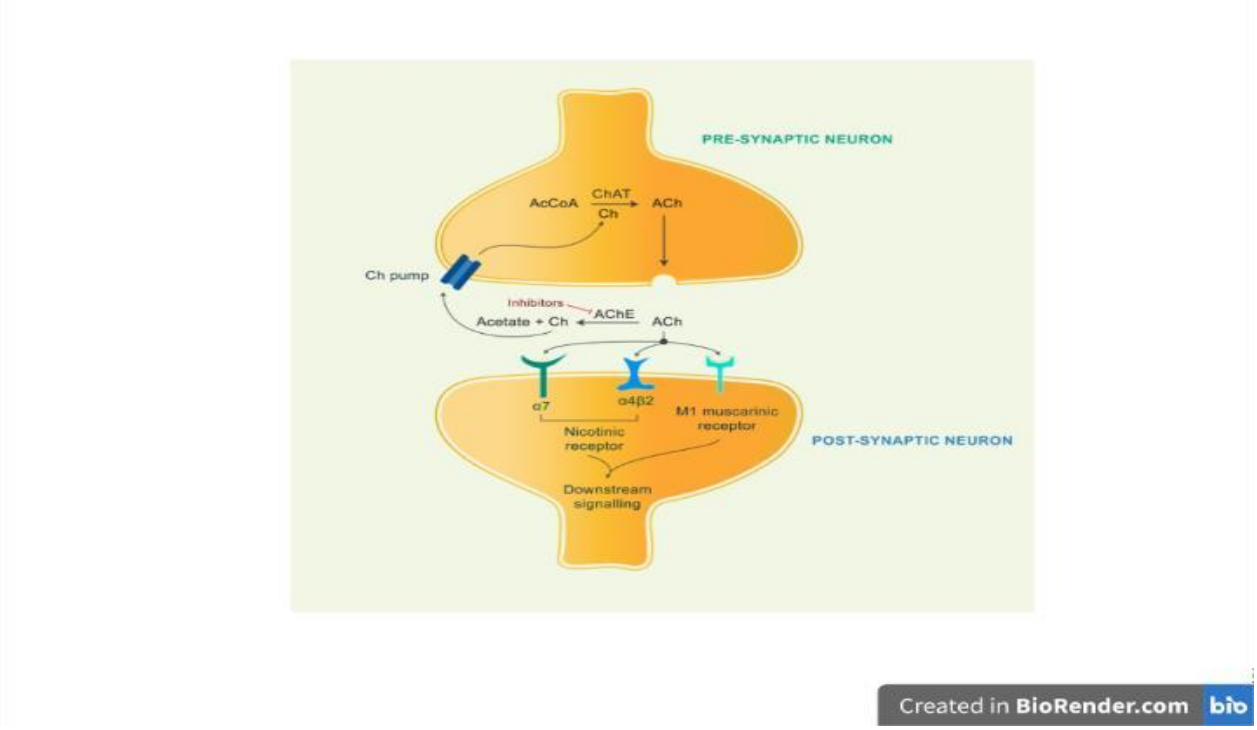


FIGURE 4: Cholinesterase Inhibitor pathway(Grossberg, 2003)

Galantamine

Galantamine is a benzazepine .Commonly , it is obtained from the Galanthus plant or other members of the Amaryllidaceae family. As a cholinesterase inhibitor, galantamine is used to mitigate the effects of gallaminetriethiodide and tubocurarine on the muscles. It has been studied in a variety of techniques for Alzheimer's and other neurological illnesses. The bioactive molecule galantamine was unintentionally discovered in the early 1950s, and plant extracts were first employed for treating nerve pain and poliomyelitis, according to the pharmacological history of Galantamine(Metz & Pavlov, 2021).The medicine exhibits dose-dependent

pharmacokinetics and a bioavailability of around 90%. By creating a bond to both the choline-binding site and the acyl-binding pocket in the active site of the anti cholinesterase enzyme in the CNS, galantamine causes a competitive and reversible inhibition of the enzyme's activity. Galantamine elevates acetylcholine in the synaptic cleft by hindering its breakdown. Galantamine has high volume of dispersion with low protein binding. In metabolism, the cytochrome P450 system is particularly complex, especially the isoenzymes CYP2D6 and CYP3A4. In urine, it seems to be 20-25 percent un-altered(Kaur et al., 2022).

Rivastigmine

A cholinesterase inhibitor, rivastigmine is used to treat mild to moderate Alzheimer's disease. Oral or transdermal patch administration is possible. Rivastigmine is a pseudo-irreversible inhibitor at it has its long-lasting effects. It's a C14H22N2O2 carbamate derivative. Once absorbed, it can create a bond with both the anionic and esteratic regions of AChE, like Ach Rivastigmine inhibits acetylcholinesterase by hydrolyzing it while leaving its esteratic site carbamylated. It has a unique structure that enables it to inhibit the AD-related G1 type of AChE. Among healthy young peopleG4 is the most prevalent isomer, although it falls with age among the patients that has AD. G1 remains stable or drops more slowly. Patients may find it more convenient to take oral rivastigmine once every three days rather than twice daily, despite the fact that this dosing schedule is associated with improved tolerability (Khoury et al., 2018).Rivastigmine is widely distributed in the body due to its low protein binding affinity (40%) and large volume of distribution (1.8-2.7 l/kg). Rivastigmine has a half-life in plasma of just 1 hour. This compound is bio-transformed by intensive first-pass metabolism into the de-carbamylated phenol NAP(Nguyen et al., 2021). Drug delivery rate in 5, 10 and 15 minutes is given on Table 1.

Table 1: Drug Delivery Rate of Rivastigmine(Di Stefano et al., 2011).

Patch Diameter	Amount of Rivastigmine	Drug delivery rate
5	9	4.6
10	18	9.5
15	27	13.3

Donepezil

Donepezil was first introduced as a choline esterase inhibitorin 1997.It achievedUSFDA authorization to be used for the treatment of Alzheimer's disease because it stimulates cholinergic activity by decelerating acetylcholine clearance in the brain. For mild to severe AD, start with a daily dose of 5mg and increase to 10 mg after four to six weeks. DPH is soluble in chloroform, glacial acetic acid, and water (55 g/L at 25 C),8.9pKatertiary amine. It is reported that the melting point tis 224 ◦C as per thermal analysis(Sutthapitaksakul et al., 2021).Donepezil inhibits acetylcholinesterase selectively and reversibly. This drug's fundamental and vital pharmacological activities may be due to enzyme inhibition, which enhances cholinergic transmission and improves Alzheimer's symptoms. In addition to the foregoing, donepezil can oppose glutamate-induced excitatory transmission by downregulating NMDA receptors and regulate amyloid proteins, which have vital impacts on Alzheimer's. Donepezil may also block inflammatory signaling pathways to provide neuroprotection. Only donepezil is approved to treat mild, moderate, and severe AD. Donepezil has a lengthy half-life that allows once-daily dosage, increased tolerability due to central AChE inhibition, no substantial dietary effects on pharmacokinetics, and minimal medication interactions .When compared to other medications, donepezil has a 100% relative oral bioavailability and is therefore well-absorbed when taken orally (Adlimoghaddam et al., 2018). Peripheral cholinergic effect of Rivastigmine, Donepezil and Galantamine is illustrated on Figure 5.

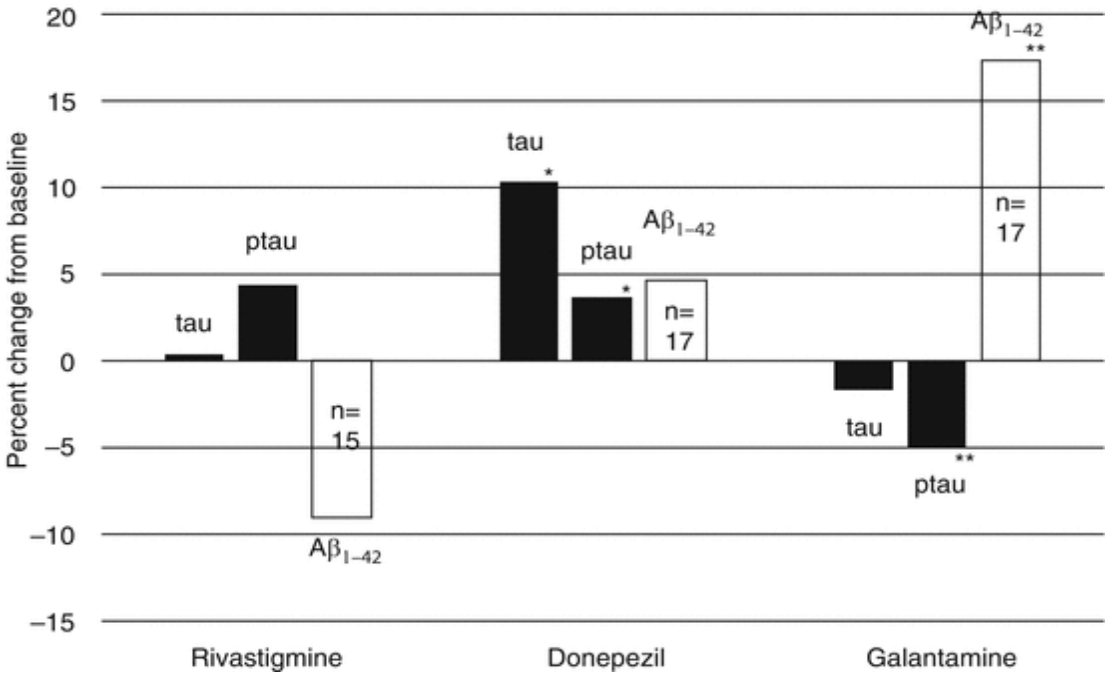


Figure 5: Peripheral Cholinergic Effect of Rivastigmine, Donepezil and Galantamine (Wilkinson et al., 2004).

Monoamine Oxidase Inhibitor

MAOI is a mitochondrial-bound enzyme found in neural and GI tissues. It has two isoforms which is MAO-A and MAO-B. These isoforms have similar sequences but distinct substrate-inhibitor locations and tissue distribution. They catalyze monoamine oxidative deamination and metabolize neurotransmitters (Manzoor&Hoda, 2020). MAO inhibitors protect against AD by: MAO inhibitors improve cognitive impairment by correcting chemical imbalances in the brain; chelators can control Aβ buildup, protect against tau hyper-phosphorylation, and prevent metal-associated oxidative stress, giving them promising anti-AD medications. APP and Aβ processing regulation(Cai, 2014). MAO inhibition is used as a potential target in AD.MAO-B activity increases with age and in AD patients, causing an increase in neurotoxic free radicals. MAO inhibitory activity is a possible biomarker for AD disease-modifying drugs (Bolea et al., 2013).It

has been shown that monoamine oxidase A (MAO-A) inhibitors are efficient antidepressants, while monoamine oxidase B (MAO-B) blockers have been addressed in the treatment of Alzheimer's. About 80% of the human brain's MAO activity is controlled by MAO-B, and it is found mostly in the striatum (Riederer et al., 2004). Monoamine oxidase inhibitor is illustrated on Figure 6.

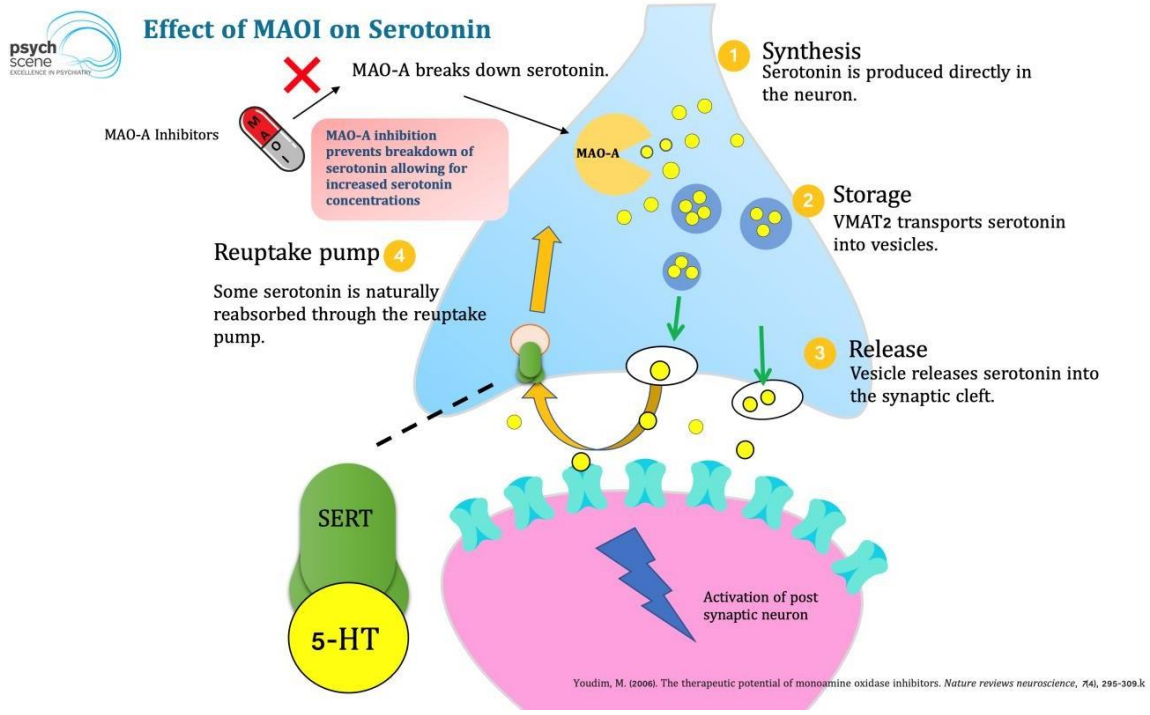


Figure 6: Monoamine Oxidase Inhibitors (Ostadkarampour&Putnins, 2021).

Selegiline

Selegiline is a monoamine oxidase inhibitor. It functions as alpha-tocopherol and has been shown to help Alzheimer's patients. Due to its ability to block oxidative deamination, selegiline also functions as an antioxidant, protecting neurons from harm. Animal studies have linked the medicine to an extension of the active lives of the animals treated with it. Selegiline has a wide range of neuro-protective effects. There is almost seven potential mechanisms exist via which

selegiline can protect against neuro-degeneration. To begin with, blocking MAO-B in the brain may reduce the production of free radicals during the usual metabolism of biogenic amines, particularly dopamine. An elevated level of MAO-B activity was detected in Alzheimer's disease and other forms of neurodegeneration(Riederer et al., 2004).Anti-neurotoxic selegiline may be neuroprotective. Selegline prevents neuronal injury by inhibiting nerve ending absorption. Selegiline metabolites inhibit absorption more than the parent molecule. MAO-B inhibition may lower oxidative stress and neurodegeneration, slowing the progression of disease. Neuro-modulatory amines can be regulated with MAO-B inhibition. Selegiline, an irreversible MAO-B inhibitor, improves cognitive function in AD patients(Behl et al., 2021).

4.4.2 TV 3326

TV 3326 is a propargylamine group that contains aminoindan.TV 3326 improves depression, boosts cholinergic transmission, and prevents ROS production and consequences. The neuroprotective agent TV 3326 has been shown to be effective in both in in vitro and in vivo studies of neurodegeneration. In vivo investigations showed that taking TV 3326 once daily for 14 days at a dose of 26 mg/kg prevented striatal dopamine decrease. TV 3326 can improve animal cognitive deficits. TV 3326 also prevents hippocampus cell damage caused by global ischaemia in gerbils and cerebral edema in mice, restoring their memory and motor capabilities. It inhibits BuChE and AChE. TV 3326 is longer-lasting and slower-acting. This antidepressant specifically suppresses MAO-A and MAO-B in the brain. In mice, TV 3326 can prevent the neurotoxic MPTP-induced decline in striatal dopamine. It can assist preserve dopamine levels in Alzheimer's patients.OS and gliosis are known to be present in neurodegenerative diseases like Alzheimer's disease (Uddin et al., 2020).

BACE-1 INHIBITORS

Aspartyl protease BACE1 is a transmembrane enzyme which pierces APP at the β-site.BACE1 andβ -secretase sequentially cleave APP to produce Aβ peptide in the brain. BACE1 is an AD

therapy target. Amyloidogenicsecretases are important AD treatment targets. Several studies suggest BACE1 inhibitors could reduce brain concentrations and slow AD progression. To further understand how BACE1 inhibitors work, it is helpful to look at the key functional units that engage with catalytic dyad. Developing BACE1 inhibitors is difficult. First, because BACE1 is located in the brain and in the interior of endosomes, it is inaccessible unless inhibitors can pass the blood-brain barrier (BBB) and neural membrane to reach the target (Pacha et al., 2019).When designing BACE1 inhibitors, it is important to take into account catalytic aspartic dyad, morphological plasticity, and large binding pocket of the enzyme. Although the inhibitors effectively decrease brain Aβ levels, they have yet to going to be useful in cognitive function in clinical studies including individuals with mild to moderate AD, raising questions about the value of these putative anti-AD medications and the design of the trials themselves(Coimbra et al., 2018).

CHAPTER 5

Stem Cell Therapy

Stem cell treatment offers a novel strategy for dealing with Alzheimer's disease. Mesenchymal stem cell therapy involves intravenous administration of stem cells throughout the body. Large doses of these stem cells can detect inflammation and restore the body. Because of this special quality, stem cells may one day be used to treat Alzheimer's disease. No known way to stop or reverse Alzheimer's disease is currently available, and researchers have not found a cure. One of the most promising treatments for Alzheimer's disease in recent decades has been stem cell therapy(Karvelas et al., 2022). Stem cell therapy for Alzheimer’s disease is shown on Figure 7.

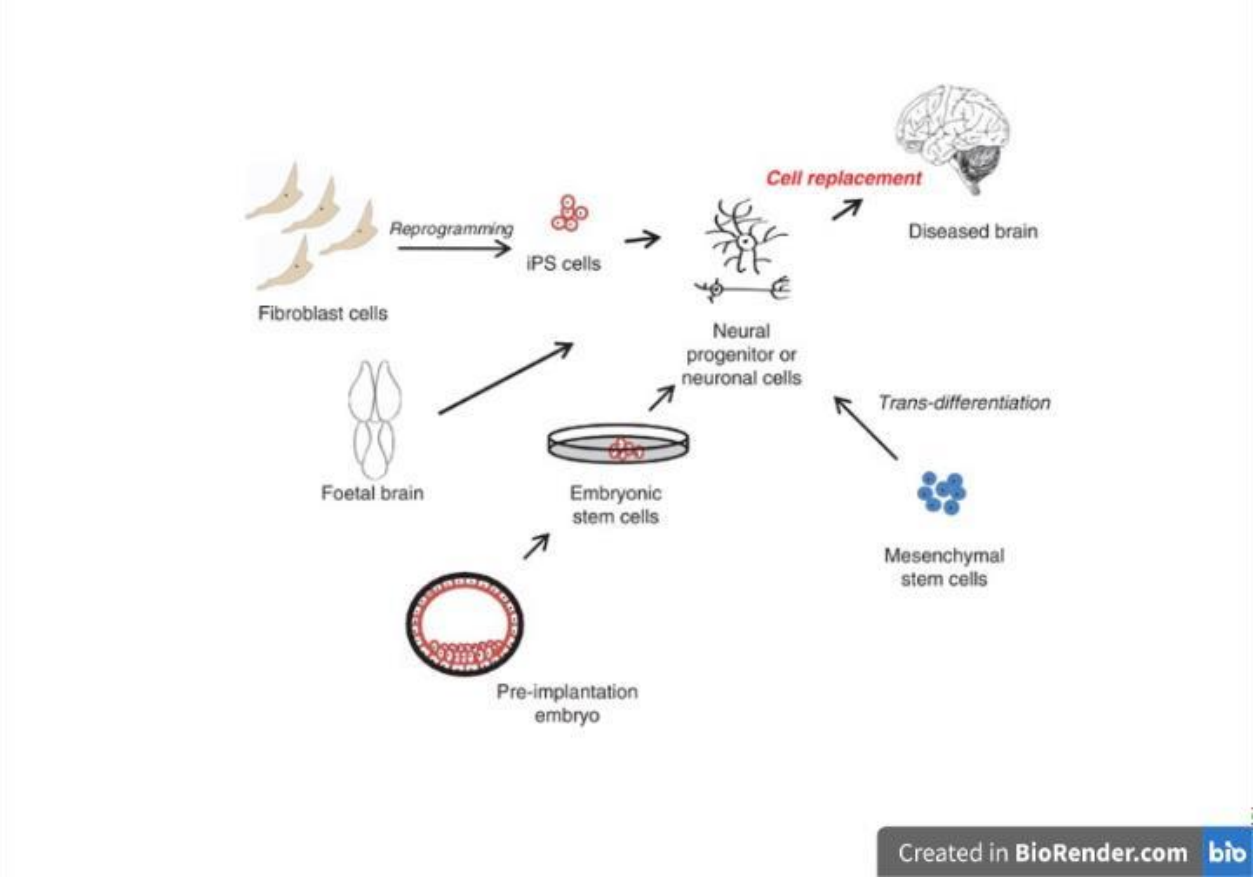


Figure 7: Stem Cell therapy for Alzheimer's disease(Karvelas et al., 2022).

Mesenchymal Stem Cell Therapy

Bone marrow, adipose, bone, Wharton's jelly, cord blood, and even peripheral blood can all be extracted for their adult stem cells, generally termed as mesenchymal stem cells. MSCs have a greater differentiation potential than some other stem cells and can respond to growth factor stimulation to become brain cells, osteocytes, chondrocytes, even adipocytes. Furthermore, MSCs seldom cause an immune response and have a low potential to develop into cancer cells(Hernández & García, 2021). Mesenchymal stem cell therapy is shown on Figure 8.

.

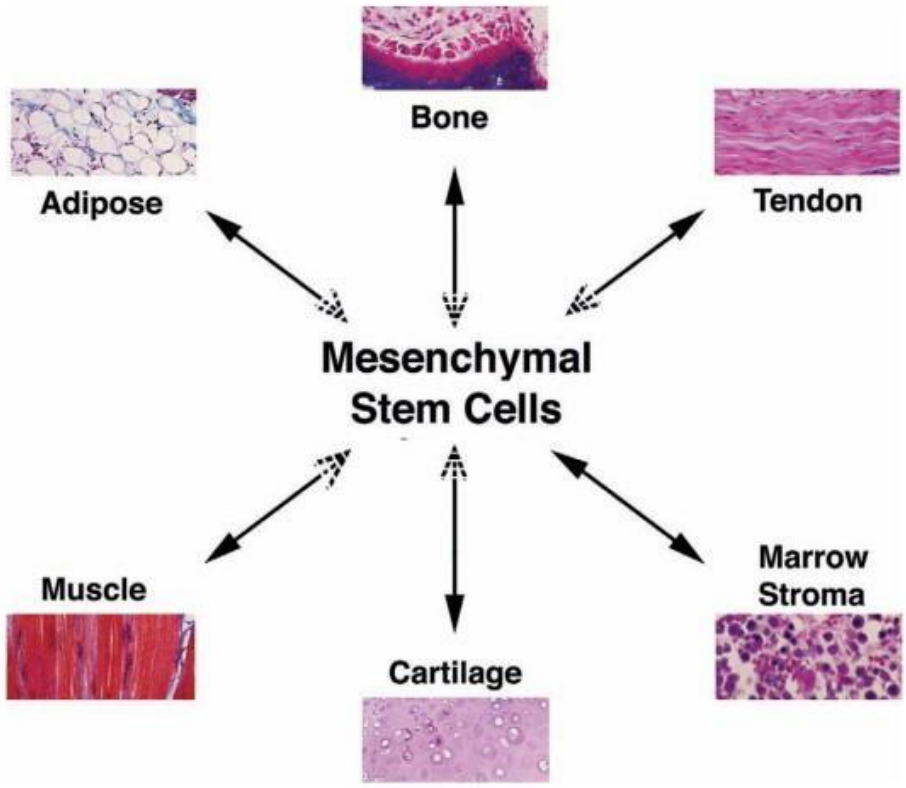


Figure 8: Mesenchymal Stem Cell (Ding et al., 2011).

Induced Pluripotent Stem Cells

Human pluripotent stem cells aid tissue regeneration. They can grow into diverse tissues or organs during transplantation. hPSCs are obtained from surplus IVF embryos. Embryonic stem cell-derived tissue has been tested in clinical trials(Yefroyev et al., 2022).iPSCs can be used for cell therapy and to develop in vitro AD brain models. Donor iPSCs carry same genotype as the donor, making them ideal for examining the effects of genetic variations on disease and developing customized treatments for exact genetic variants. Individual differences in genetic makeup have a significant impact on treatment response due to their influence on the pathogenesis of Alzheimer's disease (Yefroyev et al., 2022). Induced pluripotent stem cells have been shown on Figure 9.

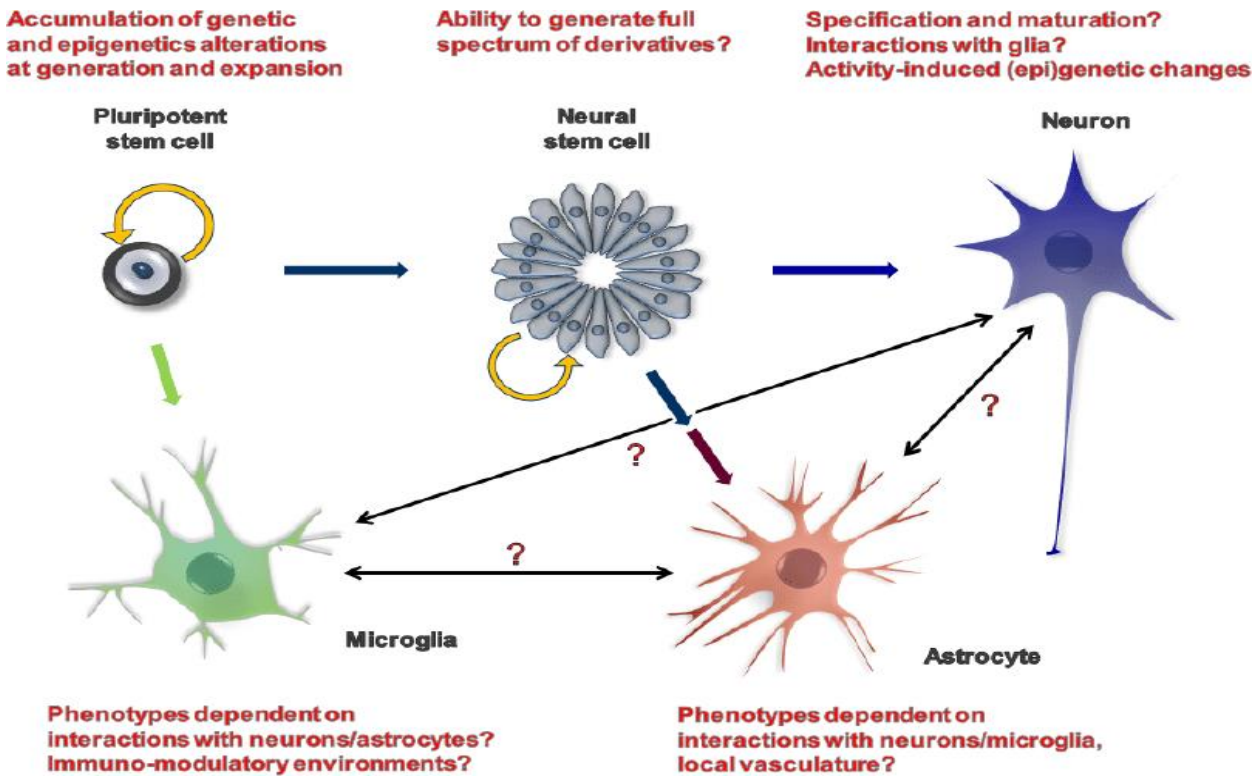


Figure 9: Induced Pluripotent Stem Cells (Asgari et al., 2010).

Risk and Challenges

Genetic mutations are possible. Applying autologous stem cell-derived tissues to treat the familial type of Alzheimer's disease is challenging since these cells carry the patient's disease-causing genes. Unmodified implants may be ineffective. may generate unexpected lineages or expand uncontrollably after implantation, producing host problems. Undifferentiated cell contamination is an issue Scientists are still studying on tiny technical challenges to pave the path for efficient AD treatment and boost progress(Liu et al., n.d.).

Clinical Trial

It is only recently that stem cell transplantation has been used to treat Alzheimer's disease. To date, there have been a lot of investigations on stem cell therapies as a remedy for AD, but mostly of are preclinical studies. However, clinical trials have also been performed in recent years. MSCs, which can be produced from a number of different tissues, were used in all six of the examined clinical studies of cell treatments. These clinical trials largely made use of intravenous administration of stem cells, with one transplantation procedure including surgical incision. MSCs have been used extensively in a wide variety of research projects because of their demonstrated durability, safety, and efficacy. Research has shown that mesenchymal stem cells (MSCs) can promote tissue regeneration, alter their surrounding milieu through paracrine actions, and modulate the immune system without increasing the risk of immunological rejection following xenotransplantation or allotransplantation.As the safety and effectiveness of MSCs have been extensively researched, their clinical benefits should enhance AD stem cell therapy(Jun Chan et al., 2021).

Improvements

Alzheimer’s disease and its underlying pathology are critical for developing disease-modifying medications. Since small oligomers are considered to be responsible for neurotoxicity and synaptotoxicity in Alzheimer disease, medication research efforts have focused on inhibiting Aβ aggregation by addressing these particles (Corbett et al., 2012). Highly accurate diagnostic measures of AD amyloid plaques and tau tangles have been available for several years, and more recently, simple blood tests have been developed (Dokholyan et al., 2022).

CHAPTER 6

Gene Therapy

Gene therapy involves genetically modifying cells to achieve a therapeutic effects or treating disease by synthesizing or repairing damaged genetic material. Gene therapy involves siRNA, shRNA, and miRNA gene silencing (Amado & Davidson, 2021).Gene therapy is a promising method of treating numerous diseases, including Alzheimer's disease. Gene therapy can stimulate enzymatic activity and replace bioactive material (Nilsson et al., 2010).In many ways, gene therapy is superior to conventional medical practices. In general, it is a drug delivery system, but it possesses desirable properties that make it an effective method of treating Alzheimer's disease. The most notable advantage of gene therapy is the ease with which genes can be introduced into the body using a virus as the vehicle for doing so. This allows us to bypass the blood-brain barrier by stimulating brain cells to generate the medicine directly. In the case of Alzheimer's, it would be possible to get the drug produced within the brain itself (Sudhakar & Richardson,2018).

AD Treatment Based on Gene-Modified Cells

Before transplanting stem cells, it can be helpful to change their genes in order to make them live longer and work better. Also, modified cells could be used to deliver factors that can help people with neurological disorders feel better. Some scientists have attempted to alter the genes of existing cells so that they produce acetylcholine. Choline acetyltransferase was put into a primary fibroblast cell line by changing its genes. After being transplanted into the hippocampus of rats, they showed that they could make Ach. One of these factors is the human nerve growth factor, which has been demonstrated to recover cholinergic neurons in rodent and primate brains

and to boost the function of cholinergic neurons. They can also generate growth factors that enhance memory and cell function (Glat & Offen, 2013). Gene modified cell based therapy is illustrated on Figure 10.

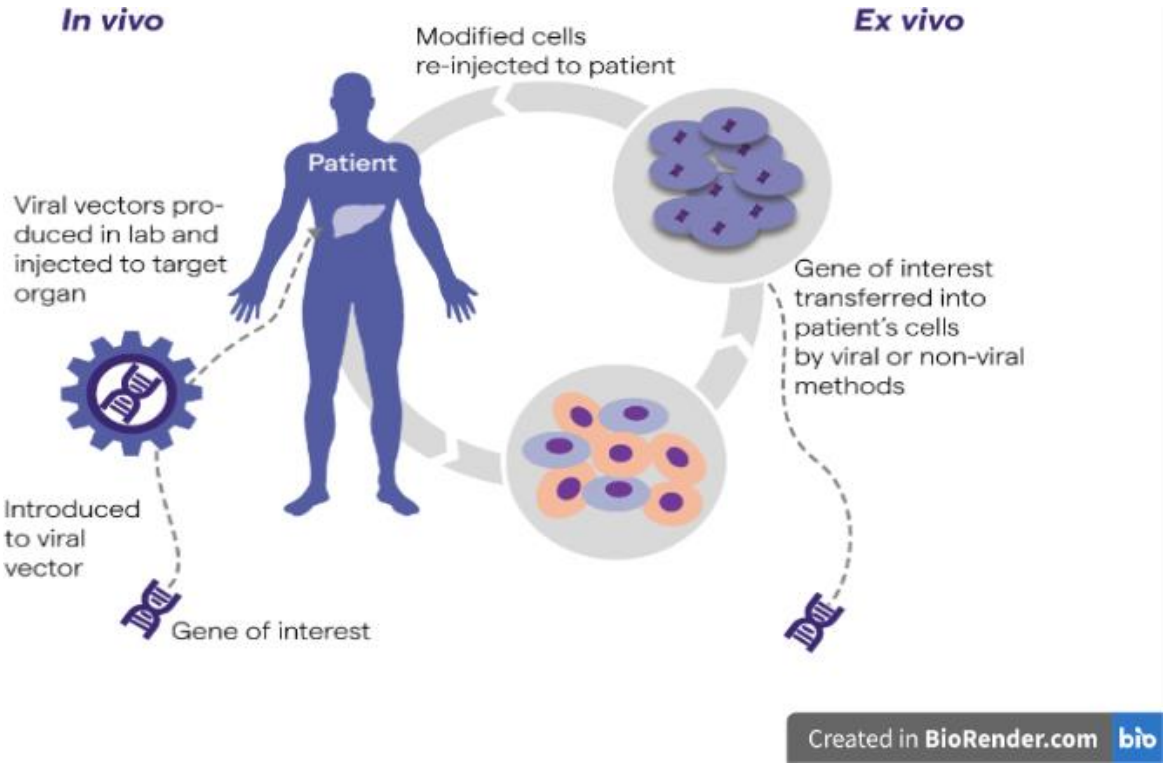


Figure 10: Gene modified cell based therapy for AD(Eshraghi et al., 2022).

Nerve Growth Factor Gene Therapy

Alzheimer is a neurological condition affecting 50 million people on a global scale. Amyloid modifying therapies may inhibit disease progression. In amyloid-overexpressing mice, elderly

rats and primates, nervous system growth factors prevent neuronal death. Nerve growth factor and Brain-derived neuro-trophic factors were two of 50 nervous system growth factors relevant to AD(Tuszynski et al., 2015). NGF inhibits the death of basal forebrain and promotes their activity. It resides in human brain and influences the neurological system of various species, including primates. AD reduces basal forebrain NGF levels. BDNF inhibits the death of cortical neurons and increases their activity. Although BDNF models for AD have been around for longer, NGF models for AD were initiated a decade earlier, and clinical trials in AD were conducted first based upon preclinical safety and effectiveness investigations. For achieving this purpose, gene therapy is one of a few options(Tuszynski et al., 2015).

Autophagy Modulation Strategy for the treatment of AD

Autophagy is the main and most essential process inside cells that gets rid of clumped proteins and damaged organelles. Autophagy modulation has become a very interesting way to treat Alzheimer's disease (AD). Protein aggregation and defective autophagy appear to form a vicious cycle in Alzheimer's disease. Recently, autophagy was suggested as a possible treatment for Alzheimer's disease. . So far, there have been two different ways to change autophagy in the CNS: small molecule therapies and genetic interventions. Targeting autophagy as a way to treat Alzheimer's disease (AD) has gotten a lot of attention .However, it takes a lot of time and resources to produce new therapeutics (Eshraghi et al., 2022).

The role of Microglia and Neuroinflammation

Alzheimer's disease is caused by neuroinflammation, the stimulation of both astrocytes and microglia in the central nervous system. Brains are prone to build amyloid- plaques and tangles. A repressed neuroinflammatory response may result to Alzheimer's disease persistence by reducing neuroinflammation, increasing neuronal survival, and preserving cognition(Fu & Ip, 2022).Role of Microgila in neuro inflammation is briefly expressed on Figure 11.

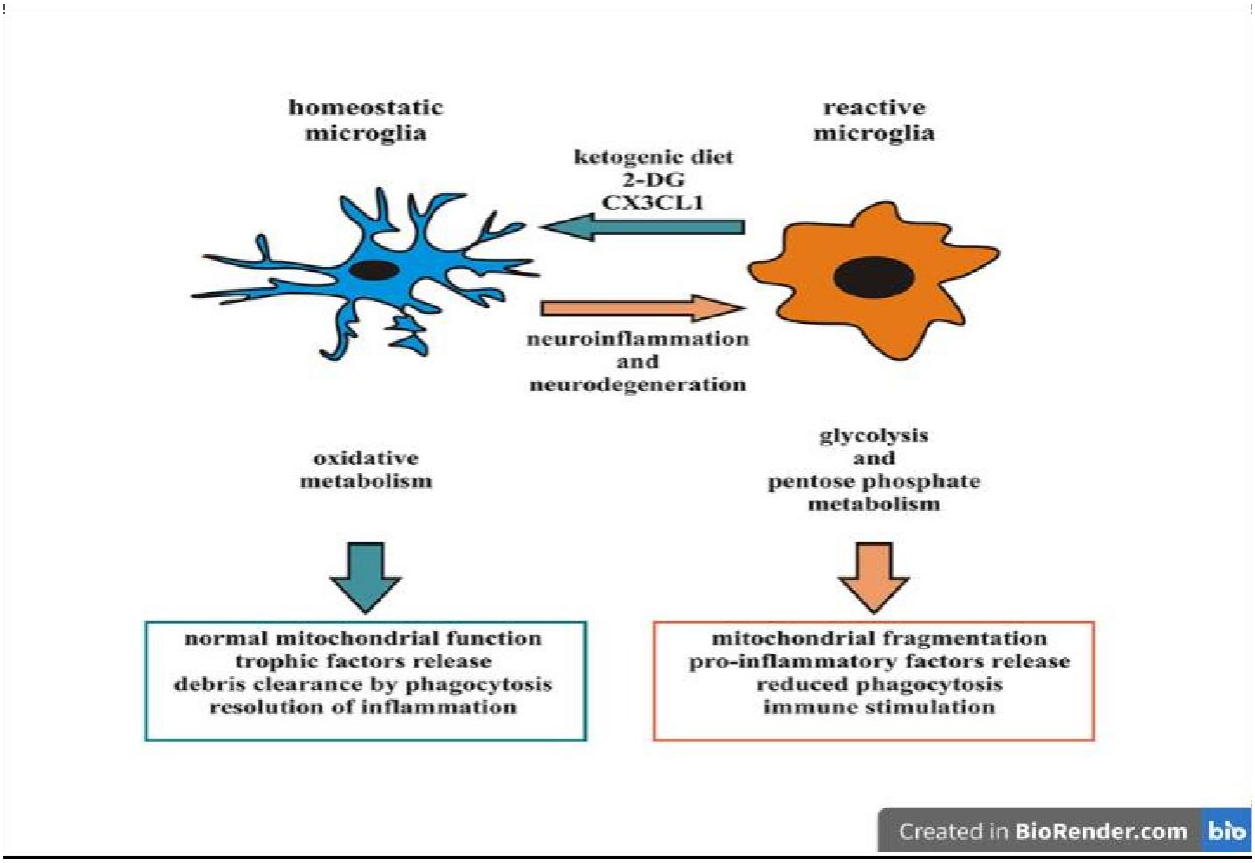


FIGURE 11: Role of Microgila in Neuroinflammation**(**Iraji et al., 2020).

Challenges

In recent decades, preclinical and clinical gene therapy experiments have been conducted to prevent or treat neurodegenerative disorders. Safety concerns remain a barrier to clinical implementation .Gene therapy toxicity can be induced by transgene overexpression in targeted or off-target cells. Poor ambulation, ataxia, dorsal root ganglion injury, and elevated transaminases are toxic effects. Host responses affect gene therapy safety and longevity. Adaptive immune systems can develop neutralizing antibodies that stop vectors from reaching their destinations. High-dose vector injections can cause insertional mutagenesis and genotoxicity. Gene-based

therapy options for neurodegenerative illnesses should be rigorously evaluated during clinical development, including effectiveness and safety and pharmacological effects (Chen et al., 2020).

Why Small Molecule Drug Therapy is better than Gene therapy

The treatment options for Alzheimer's disease include both small molecule drugs and gene therapy. Small molecule therapeutic therapies include cholinesterase inhibitors, monoamine oxidase (MAO) inhibitors, and others. Cholinesterase inhibitors have demonstrated sufficient safety and efficacy to obtain market authorization on a global scale. It guarantees increased bioavailability in contrast to other therapies. Symptomatic therapies are provided, with benefits including short-term memory enhancement and decreased cognitive impairments. It provides high efficacy and lower toxicity (Nguyen et al., 2021).Furthermore, they have a limited clinical impact because they do not tackle the underlying causes of AD or forestall cognitive decline(Iraji et al., 2020). Gene therapy, on the other hand, involves altering a patient's genes to treat an illness or improve their health in some other way, such as by correcting a genetic mutation. To treat or prevent disease, scientists have turned to gene therapy, which modifies cellular DNA. Safety concerns about gene therapy continue to be a major roadblock to its widespread clinical use. Transgene over expression in the intended tissues or expression in off target cells might cause severe toxicity, which is a risk with gene therapy. Harmful effects are difficulty walking, ataxia, impairment to the dorsal root ganglia, elevated levels of a substance called transaminases, and a decline in the sense of proprioception .As a result it can be said that using small molecule drug therapy is comparatively safer and provides better efficacy and improves the memory better than gene therapy(Chen et al., 2020b).

CHAPTER 7

Immunotherapy Of Alzheimer's Disease

Alzheimer's disease has been linked to amyloid-beta protein and the buildup of tau protein which is hyper-phosphorylated . Conventional therapies momentarily alleviate discomfort but do not address the underlying cause. Recent studies have centered on identifying the molecular and cellular mechanisms and procedures related in AD pathogenesis in an effort to boost the production of effective disease-modifying medicines(Winblad et al., 2014). Mostly immunotherapy is the researched method of Aβ-targeted therapy, supporting the current Aβ-cascade concept for the pathophysiology of AD.Preclinical models have demonstrated that passive and active immunotherapies can successfully reduce Aβ buildup and avoid subsequent disease (Winblad et al., 2014). Immunotherapy of Alzheimer's disease is briefly explained in Figure 12.

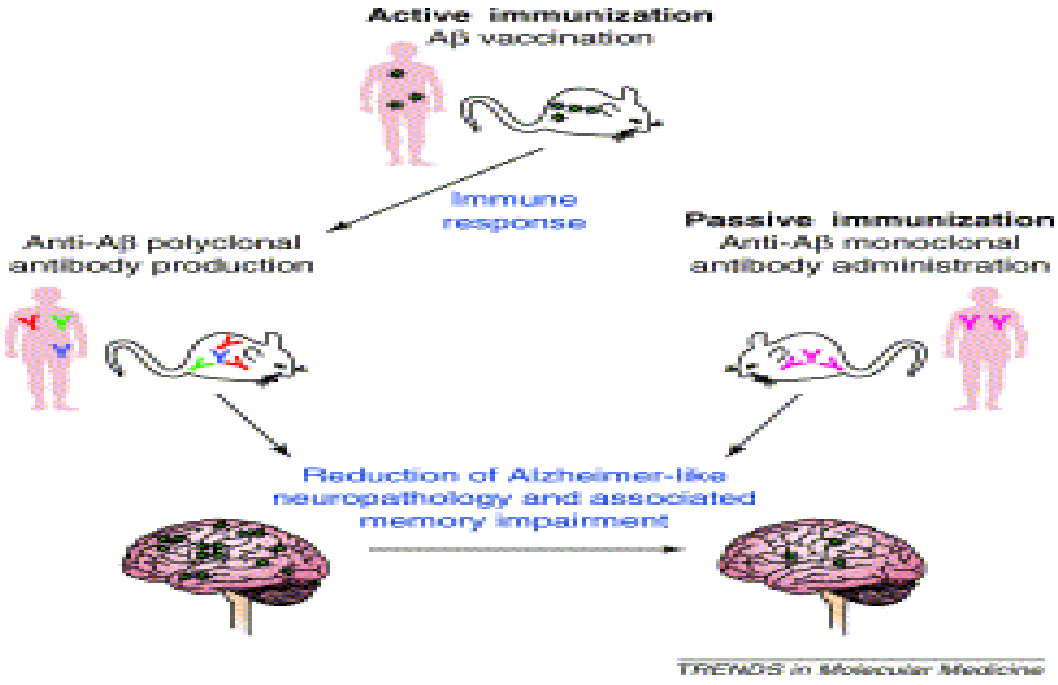


Figure 12: Immunotherapy of Alzheimer's Disease(Dodart et al., 2003).

Mechanisms of Immunotherapy Action

The effectiveness of immunotherapy for brain disorders astonished many researchers and has given the concept that the brain is immune-privileged and has little immune surveillance. This strategy assumes enough anti-body take entry to the brain and forms a bonding with amyloid so that it can activate microglia or monocyte phagocytosis. The antibody-to-Aß stoichiometry can be 1:1 and still affect deposition(Morgan, 2011).Another theory suggests that penetration of antibody into the CNS is not necessary and circulating antibodies form a "peripheral sink" which affects blood brain barrier equilibrium for Aß and it reduces the level of free Aß in blood. There appear to be processes through which circulating Aß enters the CNS, which should lessen as free Aß drops(Morgan, 2011).

Tau-Related Immunotherapy

In Alzheimer's disease (AD), there has been a recent renewed interest in immunomodulation by targeting phosphorylated tau. Tau pathology appears in the locus coeruleus before amyloid plaques, extendingto the entorhinal cortex and other brain stem nuclei. Tau is a prudent target in symptomatic AD patients because its pathology is better linked with dementia than amyloid plaque burden .Recent findings indicate that anti-tau antibodies are able to penetrate neurons through low-affinity receptors and connect in endosomes with pathogenic tau(Wisniewski &Goñi, 2015). Active tau immunization can cause encephalitis or neuronal death .Immunizing female C57BL/6 mice with recombinant tau induced neurological impairments. Tau

immunotherapy is promising but hazardous. More research is needed to determine the appropriate tau formulation and timing for focused immunotherapy(Wisniewski &Goñi, 2015).

Active Immunization

Passive and active immunotherapies are the two types of immunization process that currently exist. They are currently being looked into for the treatment of Alzheimer's right now. Even though both try to stop or slow down the loss of memory, both of them have their own benefits and drawbacks. Active immunotherapy is appealing because it can make a large number of individuals produce antibodies for a long time(Lemere, 2013).However, the danger of a harmful immune response is increased by the T cell response which is done active vaccine .An efficient vaccine will produce antibodies that react to overlapped epitopes on the protein of interest, suggesting that the vaccine has been designed to elicit a polyclonal antibody response. This is excellent for broad coverage, but not so good if the goal is to reduce a specific protein type (Lemere, 2013).

Passive Immunization

Passive immunization is the process of giving unprotected person antibodies to keep them from getting sick or to treat them if they already have it. The first official confirmation of passive immunization was when diphtheria and tetanus were cured. In this immunization newborns of guinea pigs, ferrets, chimps, and humans acquire maternal IgG primarily through placenta before birth, whereas newborns of ruminant horses and pigs are a gammaglobulinemic and obtain

maternal antibodies entirely from colostrum(Marcotte&Hammarström, 2015). Passive immunotherapy has several advantages over active forms, including the ability to stop treatment quickly in the event of adverse responses and the ability to target only the epitopes or pathogenic conformations of a protein of interest without affecting any other forms .Furthermore, chronic antibody dosage might result in the generation of anti-antibodies, which may neutralize the therapeutic efficacy of the original antibodies and cause adverse reactions such glomerulonephritis and vasculitis(Lemere, 2013).

Donanemab

Donanemab which is a humanized antibody against N-truncated pyroglutamate amyloid- peptide at position 3 (ApE3), was recently tested in a phase 2 trial for stability, tolerability, and efficacy in early Alzheimer's disease (AD) patients. The treatment slowed cognitive and neurological degradation across all secondary clinical end-points, decreased plaque burden, and tau deposition in a sub-group of patients examined by in vivo brain imaging(Bouter et al., 2022). Donanemab reduced cognitive and functional deterioration in early-stage AD patients, however secondary outcomes were mixed. Greater reductions of amyloid plaque indonanemab was linked to reduced cognitive deterioration and much less tau advancement at 24 weeks(Song et al., 2022).

UB-311 Vaccine

UB-311, an amyloid β synthetic peptide vaccine, is being tested to treat mild-to-moderate Alzheimer's patientsUB-311 has various synthetic Aβ-targeting peptides and a Th2-biased means of delivery. UB-311 is genetically diverse and responds well. In hAPP751 transgenic mice, UB-311 reduced Aβ oligomers, protofibrils, and plaque burden .This can create a highly precise molecular vaccine with a high responder rate, robust on-target immunogenicity, and cognitive enhancement, supporting UB-311 for active immunotherapy(C. Y. Wang et al., 2017).

Improvements

Alzheimer's disease can be treated using immunotherapy. Identifying targets is key to developing disease-modifying therapies for AD. The Aβ and tau theories have been proposed for years, and other mechanisms, including neuroinflammation, are connected with these two proteins.

Postmortem studies show that some AD patients have no Aβ plaques in the brain, whereas others who have plaques do not show cognitive impairment(Song et al., 2022).It's crucial to recognize Aβ and tau as disease-modifying AD targets, or to examine additional molecules that promote AD progression. Various versions of Aβ have been seen in AD patients' brains; it's important to know which type should be focused by immunotherapy for greater therapeutic benefits. Soluble Aβ oligomers are more damaging than fibrillary aggregates and correlate significantly with AD symptoms. Microglia is supposed to ingest and digest poisonous Aβ oligomers to produce thick, neurotoxic Aβ plaques. Clearing Aβ plaque rather than Aβoligomers may have minimal effect on AD cognitive impairment(Song et al., 2022).

CHAPTER 8

Drug Repositioning

The term drug repositioning refers to the investigation of existing drugs for new therapeutic purposes. It's an effective way to find or develop new pharmacological or therapeutic drug compounds .Drug repositioning conducts a vital part in enhancing the drug effectiveness(Kumar et al., 2021).AD medication discovery requires drug repositioning. It combines evidence-based treatment identification with high-throughput screening to create an innovative, efficient drug discovery workflow. The connection map (CMAP) study repositions 1,300 drug-like molecules using transcriptional profiles. Drug repositioning allows the systematic search for medicines with anti-correlated transcriptional signatures .Various compounds emerging from this analysis included licensed drugs such as the cholinesterase inhibitors Galanthamine and Tacrine(Corbett et al., 2015). Drug repositioning is briefly explained on Figure 13.

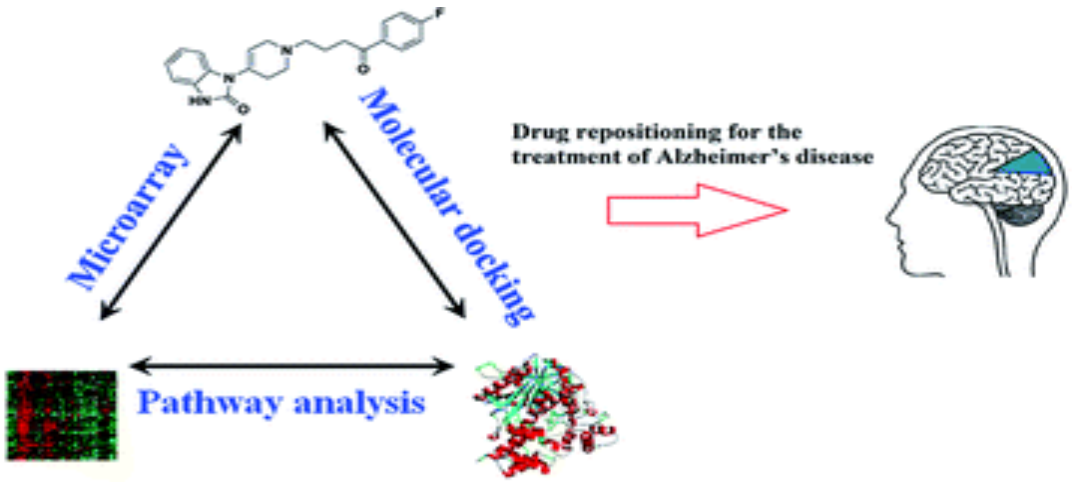


Figure 13: Drug repositioning in Alzheimer's disease(H. Xie et al., 2016).

GLP1 analogues

GLP1 analogues have a more promising scientific basis for treating AD than the other medicines now in use. Various investigations done on animal models of have showed effect of this medication on amyloid and tau pathology, hence GLP1 analogues were prioritized based on these findings (Ballard et al., 2020).Multiple studies found that treating APP-PS1 mice with liraglutide at 2 months causes reduced AD-related pathological alterations, particularly synapse degradation, neuroplasticity, and amyloid plaques. Indeed, liraglutide treatment has been consistently linked to enhanced cognition and memory in Alzheimer's disease model animals.GLP1 analogues show great promise in mitigating Alzheimer's disease(Ballard et al., 2020).

Minocycline

In compared to other tetracyclines, minocycline has the maximum lipophilicity and is therefore able to cross the blood-brain barrier with the greatest ease. Minocycline reduces Aβ aggregation

and promotes fibril disintegration in preclinical investigations. Treatment of Alzheimer's disease transgenic mice for 4 weeks or more has been shown to significantly reduce cerebral Aβ buildup and enhance behavioral outcomes in two of three trials(Corbett, Pickett, et al., 2012).

Calcium Channel Blockers

Antihypertensive drugs known as calcium channel blockers (CCBs) have been shown to have a vasodilatory impact on vascular tissue, including brain vessels. Clinical research involving calcium channel blockers and Alzheimer's disease have produced promising results. Both amlodipine and nivaldipine have shown promise in this area, with amlodipine improving memory and learning abilities in transgenic AD rats at dosages well above those allowed for therapeutic use. Further in vitro tests using therapeutically relevant dosages of either drug showed that Nivaldipine was superior than Amlodipine. Initial studies with ispradipine have also shown promise. It can be said that nivaldipine is the most promising potential CCB for treating AD (Corbett et al., 2013).

Antiepileptic Drugs

Epileptic form activity has been linked to Alzheimer's disease, and it was finalized by doing investigations on both animals and humans. Levetiracetam was the only antiepileptic medicine that successfully reduced epileptic form activity and restored cognitive impairments in human APP transgenic mice. Levetiracetam is undergoing a Phase II clinical trial for subclinical epileptic form activity improved cognition in patients with AD(Kim, 2014).

Antihypertensive Drugs

Drug repositioning can be done in various anti-hypertensive drugs. Perindopril, an ACE inhibitor has been shown to protect against memory loss in Alzheimer's disease models based on Aβ infusions and APP transgenic mice. Multiple medications, including ACE inhibitors, blockers of calcium channels and angiotensin-1 receptor blockers are all hypertension drugs that have been investigated as treatment options for Alzheimer's disease. Some of these compounds exerted antiamyloid activities in cultured cells and mouse models of AD(Kim, 2014).

Angiotensin Receptor Blockers

Angiotensin II modulates acetylcholine and inflammatory neurotransmitters. In vitro studies suggest Angiotensin channel blockers alter Angiotensin II via inhibiting the AT1 receptor and boosting Angiotensin II synthesis, which affects cognition. Several Angiotensin receptor blockers can cross the blood-brain barrier and reduce cerebral hypertension, making them possible AD drugs(Corbett et al., 2013).

Advantages of Drug Repositioning

Drug repositioning takes into consideration previously acquired data, especially on the treatment's tolerability and toxicity, which could make the earliest phases of research for a repurposed drug much faster, cheaper, and boost its marketability. The level of safety necessary for a medicine is heavily interrelated on its intention, therefore its bad effects will be proportionately fewer tolerable once repositioned for a less dangerous or severe disease(Jourdan et al., 2020).

Improvements

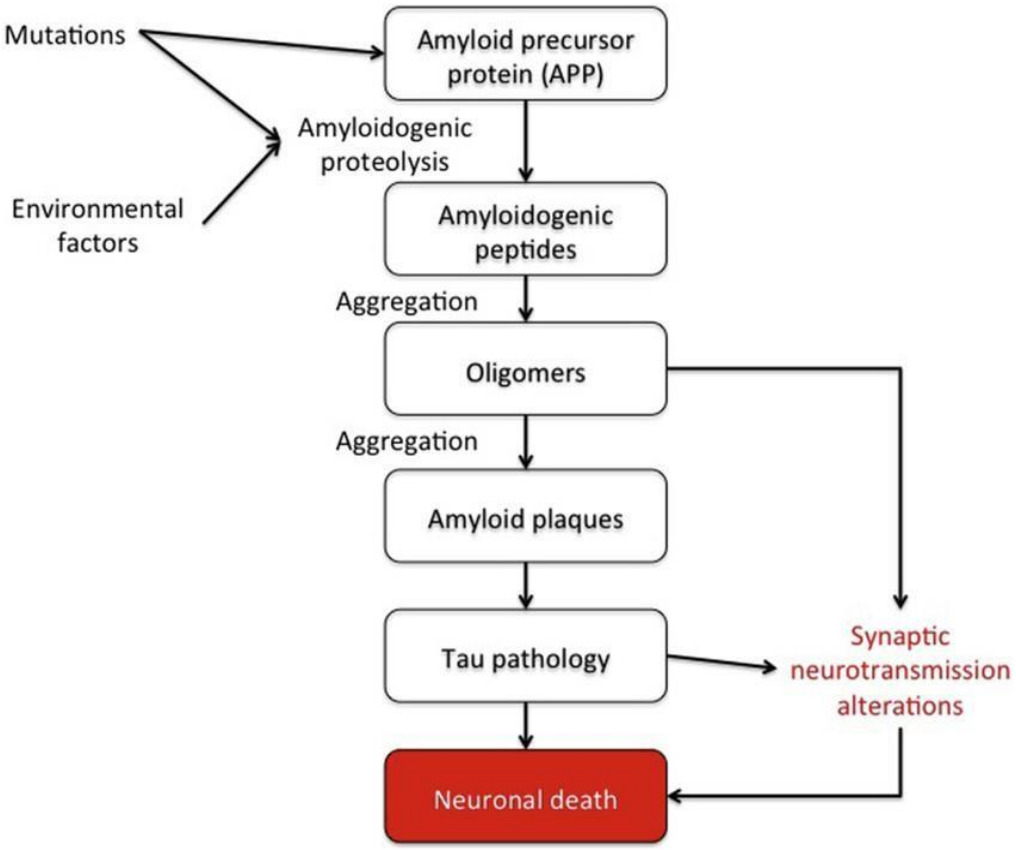
Drug repositioning has room for development in a few key areas. Researchers confront significant obstacles due to the low level of intellectual property protection provided for these medicines. The conventional methods of developing new drugs are expensive, risky, and time-consuming. As a result, drug repositioning has received a lot of attention as of lately, and with good reason: it stimulates the pace at which new medications reach the clinic (Jourdan et al., 2020). Despite the proliferation of medical databases, it is challenging to determine how to best leverage vast stores of medical information. The need for innovative strategies for medication repositioning is urgent. Another pressing problem that needs to be addressed is that of intellectual property. If these challenges are solved than drug repositioning can bring a miracle in medical science(Xue et al., 2018).

CHAPTER 9

Treatments To Promote Neuronal Function

Neuronal stability and activity depend on organelle and protein quality. Alzheimer's disease is also denoted by problems with way intracellular parts are cleared out and reused. In fact, neuronal homeostasis is made up of autophagy, mitophagy, and apoptosis. Pathological phenotypes of AD may be caused by problems with these cellular processes(Rezaeian et al., 2022).

Table 2: Neuronal mechanism in Alzheimer's disease(Coman&Nemeş, 2017).



Autophagy In Alzheimer's Disease

Autophagy is eukaryotic cells' internal breakdown and recycling mechanism. Malnutrition, illness, inflammation, and growth factor deficiency trigger autophagy. Autophagy was once assumed to involve the non-selective disintegration and regeneration of a randomized cytoplasmic portion during nutrient- or resource stress. It accumulates due to impaired fusion with lysosomes(Rezaeian et al., 2022). Autophagy in Alzheimer's disease is explained in Figure 14.

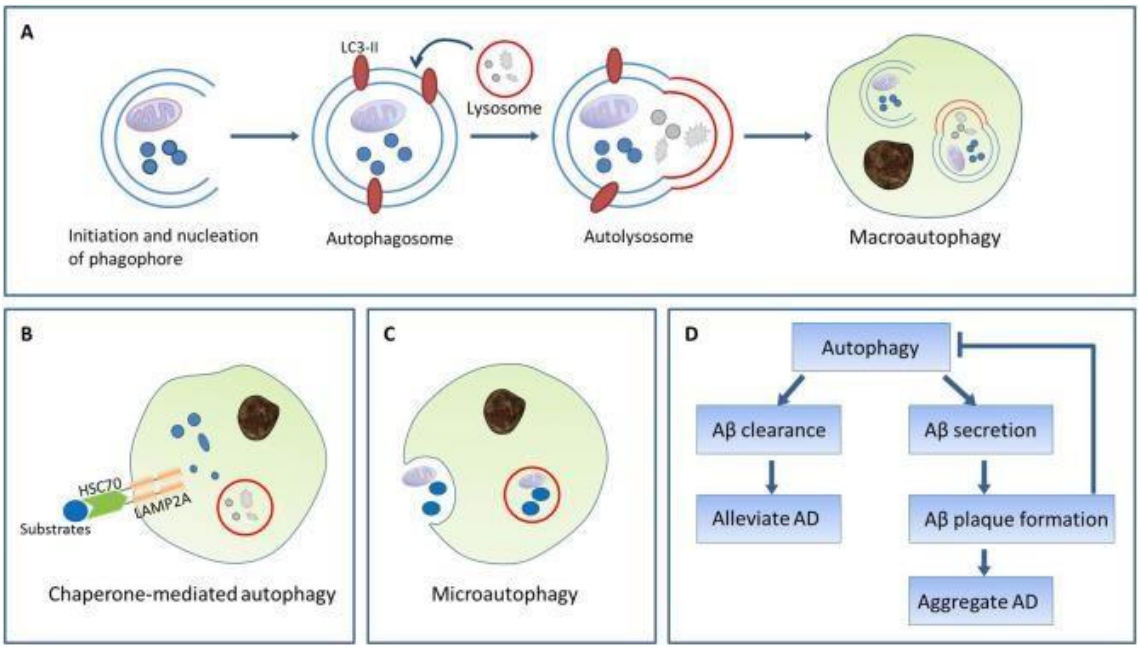


Figure 14: Autophagy in Alzheimer's disease(Zeng et al., 2019).

Presenilin Mutations

Presenilin genes cause early-onset familial Alzheimer's disease, harboring 300 causal mutations and roughly 90% of the mutations involved with an extremely aggressive disease type.PS1 and PS2 contain 67% identical sequences. Presenilin mRNAs are found in human and mouse brain, heart, kidney, and muscle. PS1 and PS2 are redundant. Myelination, synaptic function, cognitive function, and plasticity are all aided by presenilin 1, as are the preservation of neural progenitor cells, the development of new neurons, the extension of existing neurons' axons, and the formation of synapses. As a result, alterations in presenilin 1/-secretase may contribute to neurodegeneration in the early stages of Alzheimer's disease pathogenesis by causing abnormal signaling, synaptic dysfunction, impaired memory, and an elevated A42/A40 ratio(Zhang et al., 2013). AD is usually sporadic. A genetic variation involving three genes causes the illness. PSEN1 and 2 and APP are AD-related genes whose mutations cause most FAD instances. PSEN1 P117L mutation impairs NPC survival, causing reduced neurogenesis(Hernández-Sapiéns et al., 2022).

Apolipoprotein Gene

It is not fully understood how Apoe4 raises the risk of AD, although it may work by affecting Aβ aggregation and clearance, which in turn affects when Aβ deposition begins (R. Briggs et al., 2016). Other proposed mechanisms are synaptic function, neurotoxicity, tau hyper-phosphorylation, and neuroinflammation. Activation of the Apo-related protein there at blood–brain barrier may give a therapeutic target to impact Aβ clearance. Other treatment possibilities may include modulating Apoe4 levels or turning Apoe4 to Apoe3, however medical studies are currently lacking(R. Briggs et al., 2016).

Glucagon-Like Peptide-1 (GLP-1)

GLP-1 is produced in the intestine by enteroendocrine cells and secreted constantly, although at a very low baseline level. It is also synthesized by the brain and other cells and organs.GLP-1 receptor activation accelerates beta-cell proliferation and glucose-dependent insulin response in type II diabetics(Reich & Hölscher, 2022).GLP-1 protects cultured neuronal cells from excite-toxic cell death and oxidative damage. Neurons were protected from beta-amyloid cell death, iron-induced oxidative stress, including membrane lipid peroxidation. GLP-1 also protected against peripheral neuropathy. This neuroprotective function reduces kainate's neurotoxicity by mainly regulating calcium input into neurons. These results imply that GLP-1 or a similar peptide affects a number of AD therapy targets, such as decreased neural transmission, neurodegenerative processes, and impaired neuronal regeneration(Hölscher & Li, 2010).

Improvement

MTDL medicines for neurodegenerative illnesses like AD are gaining popularity. Pathophysiology and neural evolution may occur from a disruption of a complex intracellular

network. Sometimes it may not deliver intended result as it depends on single target(Rajasekhar&Govindaraju, 2018). Complicated pathophysiology of AD involves disruption of critical molecular pathways, and successful medication design must integrate numerous disease pathways. So it can be said that if molecular signaling can be improved along with biological signaling it has great potential in the field of Alzheimer's disease(Rajasekhar & Govindaraju, 2018).

CHAPTER 10

Conclusion and Future Directions

Conclusion

Alzheimer's disease is a complex, debilitating neurodegenerative disorder, with a rapidly increasing worldwide prevalence. Gene therapy, small molecule medication therapy, and stem cell therapy are only few of the popular approaches currently being explored to treat Alzheimer's disease. But none these can't totally cure this disease. It might mitigate its effect and prevent cognitive memory loss but to eradicate this disease newer intervention is needed. As a result, newer techniques like nanotechnology, personalized medicine and AI based therapies must be used in a higher extent. They are comparatively safer and more precise than other techniques and provides better efficacy as well. Since nanotechnology is developing at such a fast pace, personalized medicine is poised to demonstrate remarkable efficacy in biomedicine as a result of its exceptional biophysical features. New eras in the diagnostic and treatment process for Alzheimer's disease may be possible by the combination between nanotechnology and AI-based personalized medicine.

Future Directions

Nanotechnology

Alzheimer's disease severely impairs a person's ability to remember, think, and act normally. Although many studies and treatments have been developed to improve the detection and treatment of Alzheimer's disease, the disease is still disproportionately affecting elderly people. Nano technology can bring massive change in the field of medications used to treat AD (Chopra et al., 2022).Nano technology is a reliable option of treatment for AD. Very strong signal transduction is achieved by nanotechnology, which may prove valuable in the diagnosis of Alzheimer's. Ingeniously manufactured nano-molecules' physical (magnetic, optical, electrical), chemical, and/or physicochemical activities can be exploited in imaging/diagnostics. Alzheimer's soluble biomarkers are detected two ways. The first measures CSF or plasma tau or Aβ. Though this process produces more solid results, pathogenic markers cannot be effectively examined with conventional ELISA or western blotting procedures because their concentrations in CSF are so minimal in early Alzheimer's(Pange et al., 2022).

Artificial Intelligence

It is widely believed that AI has the capability to significantly improve Alzheimer's patients' access to care and overall quality of life. In order to better diagnose AD and anticipate its progression and conversion, it may be advantageous to apply artificial intelligence (AI) and machine learning (ML) techniques, which are very inexpensive tools with outstanding performance metrics. There's a lot of numerical methods here, particularly in the areas of probability and drawing borders by measuring distances between points(B. Xie et al., 2020).Precision medicine is a new method for treating and preventing disease that takes into account a wide variety of characteristics, which comprise the patient's lifestyle, genetics, physiology, and the patient's and the community's surroundings. If algorithms are implemented properly it can increase the precision and ability to be used as a treatment method for Alzheimer’s disease(Silva-Spínola et al., 2022).

Personalized Medicine

To maximize the success of treatment, personalized medicine bridging the gap between the therapeutic goal and the patient's actual reaction. This term describes therapies based on molecular science that can halt the development of a disease or at least significantly slow it down. Due to the wide range of possible causes and manifestations based on a person's genes, it is common practice to incorrectly categorize patients with various profiles into the same group and subject them to identical clinical treatments, despite the obvious differences between them(Carotenuto et al., 2021).Personalized medicine uses a patient's genetic history and genetic analysis to discover modifiable exposure to risk factors for AD, including overweight, hyperlipidemia, low physical activity, and smoking. Modern analysis techniques and diagnostic processes can be used for early preclinical AD diagnosis. Genetic markers can indeed be useful in clinical trial design(De Matteis et al., 2017).

References

Abbas Tahami Monfared Michael Byrnes Leigh Ann White Quanwu Zhang, A. J., Tahami Monfared, A. A., Zhang, Á. Q., & Byrnes Á L A White, M. J. (n.d.). *Alzheimer's Disease: Epidemiology and Clinical Progression*. https://doi.org/10.1007/s40120-022-00338-8

Amado, D. A., & Davidson, B. L. (2021). Gene therapy for ALS: A review. *Molecular Therapy*, *29*(12), 3345–3358. https://doi.org/10.1016/J.YMTHE.2021.04.008

Ando, K., Houben, S., Homa, M., de Fisenne, M. A., Potier, M. C., Erneux, C., Brion, J. P., & Leroy, K. (2021). Alzheimer's Disease: Tau Pathology and Dysfunction of Endocytosis. *Frontiers in Molecular Neuroscience*, *13*(January), 1–6. https://doi.org/10.3389/fnmol.2020.583755

Asgari, S., Pournasr, B., Salekdeh, G. H., Ghodsizadeh, A., Ott, M., & Baharvand, H. (2010). Induced pluripotent stem cells: A new era for hepatology. *Journal of Hepatology*, *53*(4), 738–751. https://doi.org/10.1016/j.jhep.2010.05.009

Ashford, M. T., Veitch, D. P., Neuhaus, J., Nosheny, R. L., Tosun, D., & Weiner, M. W. (2021). The search for a convenient procedure to detect one of the earliest signs of Alzheimer's disease: A systematic review of the prediction of brain amyloid status. *Alzheimer's & Dementia*, *17*(5), 866–887. https://doi.org/10.1002/ALZ.12253

Athar, T., Al Balushi, K., & Khan, S. A. (2021). Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. *Molecular Biology Reports*, *48*(7), 5629–5645. https://doi.org/10.1007/s11033-021-06512-9

Ballard, C., Aarsland, D., Cummings, J., O'Brien, J., Mills, R., Molinuevo, J. L., Fladby, T., Williams, G., Doherty, P., Corbett, A., & Sultana, J. (2020). Drug repositioning and repurposing for Alzheimer disease. *Nature Reviews Neurology*, *16*(12), 661–673. https://doi.org/10.1038/s41582-020-0397-4

Bature, F., Guinn, B. A., Pang, D., & Pappas, Y. (2017). Signs and symptoms preceding the diagnosis of Alzheimer's disease: A systematic scoping review of literature from 1937 to 2016. *BMJ Open*, *7*(8). https://doi.org/10.1136/bmjopen-2016-015746

Briggs, C. A., Chakroborty, S., & Stutzmann, G. E. (2017). Emerging pathways driving early synaptic pathology in Alzheimer's disease. *Biochemical and Biophysical Research Communications*, *483*(4), 988–997. https://doi.org/10.1016/j.bbrc.2016.09.088

Briggs, R., Kennelly, S. P., & O'neill, D. (2016). DRUG THERAPIES IN…. In *Clinical Medicine* (Vol. 16).

Carotenuto, A., Traini, E., Fasanaro, A. M., & Battineni, G. (2021). *Tele-Neuropsychological Assessment of Alzheimer ' s Disease*.

Chapleau, M., Iaccarino, L., Soleimani-Meigooni, D., & Rabinovici, G. D. (2022). The Role of Amyloid PET in Imaging Neurodegenerative Disorders: A Review. *Journal of Nuclear Medicine*, *63*(Supplement 1), 13S-19S. https://doi.org/10.2967/JNUMED.121.263195

Chen, W., Hu, Y., & Ju, D. (2020). Gene therapy for neurodegenerative disorders: advances, insights and prospects. *Acta Pharmaceutica Sinica B*, *10*(8), 1347–1359. https://doi.org/10.1016/j.apsb.2020.01.015

Chopra, H., Bibi, S., Singh, I., Kamal, M. A., Islam, F., Alhumaydhi, F. A., Emran, T. Bin, & Cavalu, S. (2022). Nanomedicines in the Management of Alzheimer's Disease: Current View and Future Prospects. *Frontiers in Aging Neuroscience*, *14*(July), 1–17. https://doi.org/10.3389/fnagi.2022.879114

Coman, H., & Nemeş, B. (2017). New Therapeutic Targets in Alzheimer's Disease. *International Journal of Gerontology*, *11*(1), 2–6. https://doi.org/10.1016/j.ijge.2016.07.003

Corbett, A., Pickett, J., Burns, A., Corcoran, J., Dunnett, S. B., Edison, P., Hagan, J. J., Holmes, C., Jones, E., Katona, C., Kearns, I., Kehoe, P., Mudher, A., Passmore, A., Shepherd, N., Walsh, F., & Ballard, C. (2012). Drug repositioning for Alzheimer's disease. *Nature Reviews Drug Discovery*, *11*(11), 833–846. https://doi.org/10.1038/nrd3869

Corbett, A., Smith, J., & Ballard, C. (2012). New and emerging treatments for Alzheimers disease. In *Expert Review of Neurotherapeutics* (Vol. 12, Issue 5, pp. 535–543). Expert Reviews Ltd. https://doi.org/10.1586/ern.12.43

Corbett, A., Williams, G., & Ballard, C. (2013). Drug Repositioning: An Opportunity to Develop Novel Treatments for Alzheimer's Disease. *Pharmaceuticals 2013, Vol. 6, Pages 1304-1321*, *6*(10), 1304–1321. https://doi.org/10.3390/PH6101304

Corbett, A., Williams, G., & Ballard, C. (2015). Drug repositioning in Alzheimer's disease. *Frontiers in Bioscience - Scholar*, *7S*(1), 184–188. https://doi.org/10.2741/s432

De Matteis, L., Martín-Rapún, R., & de la Fuente, J. M. (2017). Nanotechnology in Personalized Medicine: A Promising Tool for Alzheimer's Disease Treatment. *Current Medicinal Chemistry*, *25*(35), 4602–4615. https://doi.org/10.2174/0929867324666171012112026

Di Stefano, A., Iannitelli, A., Laserra, S., & Sozio, P. (2011). Drug delivery strategies for Alzheimer's disease treatment. *Expert Opinion on Drug Delivery*, *8*(5), 581–603. https://doi.org/10.1517/17425247.2011.561311

Ding, D. C., Shyu, W. C., & Lin, S. Z. (2011). Mesenchymal stem cells. *Cell Transplantation*, *20*(1), 5–14. https://doi.org/10.3727/096368910X

Dodart, J. C., Bales, K. R., & Paul, S. M. (2003). Immunotherapy for Alzheimer's disease: Will vaccination work? *Trends in Molecular Medicine*, *9*(3), 85–87. https://doi.org/10.1016/S1471-4914(03)00022-4

Eshraghi, M., Ahmadi, M., Afshar, S., Lorzadeh, S., Adlimoghaddam, A., Rezvani Jalal, N., West, R., Dastghaib, S., Igder, S., Torshizi, S. R. N., Mahmoodzadeh, A., Mokarram, P., Madrakian, T., Albensi, B. C., Łos, M. J., Ghavami, S., & Pecic, S. (2022). Enhancing autophagy in Alzheimer's disease through drug repositioning. *Pharmacology & Therapeutics*, *237*, 108171. https://doi.org/10.1016/J.PHARMTHERA.2022.108171

Fan, L., Mao, C., Hu, X., Zhang, S., Yang, Z., Hu, Z., Sun, H., Fan, Y., Dong, Y., Yang, J., Shi, C., & Xu, Y. (2020). New Insights Into the Pathogenesis of Alzheimer's Disease. *Frontiers in Neurology*, *10*(January), 1–12. https://doi.org/10.3389/fneur.2019.01312

Fu, W.-Y., & Ip, N. Y. (2022). The role of genetic risk factors of Alzheimer's disease in synaptic dysfunction. *Seminars in Cell & Developmental Biology*. https://doi.org/10.1016/J.SEMCDB.2022.07.011

Glat, M. J., & Offen, D. (2013). Cell and gene therapy in alzheimer's disease. *Stem Cells and Development*, *22*(10), 1490–1496. https://doi.org/10.1089/scd.2012.0633

Govindpani, K., Vinnakota, C., Waldvogel, H., Faull, R., & Kwakowsky, A. (2020). Vascular dysfunction in Alzheimer's disease: A biomarker of disease progression and a potential therapeutic target. *Neural Regeneration Research*, *15*(6), 1030–1032. https://doi.org/10.4103/1673-5374.270306

Hernández-Sapiéns, M. A., Reza-Zaldívar, E. E., Márquez-Aguirre, A. L., Gómez-Pinedo, U., Matias-Guiu, J., Cevallos, R. R., Mateos-Díaz, J. C., Sánchez-González, V. J., & Canales-Aguirre, A. A. (2022). *Presenilin mutations and their impact on neuronal differentiation in Alzheimer's disease*. https://doi.org/10.4103/1673-5374.313016

Hernández, A. E., & García, E. (2021). *Mesenchymal Stem Cell Therapy for Alzheimer's*

Disease. https://doi.org/10.1155/2021/7834421

Hölscher, C. (2014). The incretin hormones glucagonlike peptide 1 and glucose-dependent insulinotropic polypeptide are neuroprotective in mouse models of Alzheimer's disease. *Alzheimer's and Dementia*, *10*(1 SUPPL.). https://doi.org/10.1016/j.jalz.2013.12.009

Hölscher, C., & Li, L. (2010). New roles for insulin-like hormones in neuronal signalling and protection: New hopes for novel treatments of Alzheimer's disease? *Neurobiology of Aging*, *31*(9), 1495–1502. https://doi.org/10.1016/j.neurobiolaging.2008.08.023

Iqbal, K., Del C. Alonso, A., Chen, S., Chohan, M. O., El-Akkad, E., Gong, C. X., Khatoon, S., Li, B., Liu, F., Rahman, A., Tanimukai, H., & Grundke-Iqbal, I. (2005). Tau pathology in Alzheimer disease and other tauopathies. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1739*(2), 198–210. https://doi.org/10.1016/j.bbadis.2004.09.008

Ji, C., Xue, G. F., Li, G., Li, D., & Hölscher, C. (2016). Neuroprotective effects of glucose-dependent insulinotropic polypeptide in Alzheimer's disease. *Reviews in the Neurosciences*, *27*(1), 61–70. https://doi.org/10.1515/revneuro-2015-0021

Jourdan, J.-P., Bureau, R., Rochais, C., Dallemagne, P., & Jean-Pierre Jourdan, C. (2020). *Drug repositioning: a brief overview*. https://doi.org/10.1111/jphp.13273

Jun Chan, H., Roy, J., Lim Tipoe, G., Fung, M.-L., Wei Lim, L., Borlongan, C., & Napoli, E. (2021). *Molecular Sciences Therapeutic Potential of Human Stem Cell Implantation in Alzheimer's Disease*. https://doi.org/10.3390/ijms221810151

Karvelas, N., Bennett, S., Politis, G., Kouris, N. I., & Kole, C. (2022). Advances in stem cell therapy in Alzheimer's disease: a comprehensive clinical trial review. *Stem Cell Investigation*, *9*. https://doi.org/10.21037/SCI-2021-063/COIF

Kim, T.-W. (2014). *Drug Repositioning Approaches for the Discovery of New Therapeutics for Alzheimer's Disease*. https://doi.org/10.1007/s13311-014-0325-7

Kocahan, S., & Doğan, Z. (2017). Mechanisms of Alzheimer's disease pathogenesis and prevention: The brain, neural pathology, N-methyl-D-Aspartate receptors, tau protein and other risk factors. *Clinical Psychopharmacology and Neuroscience*, *15*(1), 1–8.

https://doi.org/10.9758/cpn.2017.15.1.1

Kumar, A., Das, K., Sharma, D., & Sharma, L. (2021). *Drug repurposing strategy for treating Alzheimer's disease*. https://doi.org/10.1002/alz.058503

Kurz, C., Walker, L., Rauchmann, B. S., & Perneczky, R. (2022). Dysfunction of the blood–brain barrier in Alzheimer's disease: Evidence from human studies. *Neuropathology and Applied Neurobiology*, *48*(3), 1–12. https://doi.org/10.1111/nan.12782

Lee, A. J., Raghavan, N. S., Bhattarai, P., Siddiqui, T., Sariya, S., Reyes-Dumeyer, D., Flowers, X. E., Cardoso, S. A. L., De Jager, P. L., Bennett, D. A., Schneider, J. A., Menon, V., Wang, Y., Lantigua, R. A., Medrano, M., Rivera, D., Jiménez-Velázquez, I. Z., Kukull, W. A., Brickman, A. M., … Mayeux, R. (2022). FMNL2 regulates gliovascular interactions and is associated with vascular risk factors and cerebrovascular pathology in Alzheimer's disease. *Acta Neuropathologica*, *144*(1), 59–79. https://doi.org/10.1007/s00401-022-02431-6

Liu, X.-Y., Yang, L.-P., & Zhao, L. (n.d.). *World Journal of Stem Cells Stem cell therapy for Alzheimer's disease Conflict-of-interest statement*. https://doi.org/10.4252/wjsc.v12.i8.787

Mayeux, R., & Stern, Y. (2012). Epidemiology of Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(8). https://doi.org/10.1101/CSHPERSPECT.A006239

Mehta, D., Jackson, R., Paul, G., Shi, J., & Sabbagh, M. (n.d.). *Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015*. https://doi.org/10.1080/13543784.2017.1323868

Mielke, M. M. (n.d.). *Sex and Gender Differences in Alzheimer's Disease Dementia*.

Misrani, A., Tabassum, S., & Yang, L. (2021). Mitochondrial Dysfunction and Oxidative Stress in Alzheimer's Disease. *Frontiers in Aging Neuroscience*, *13*(February), 1–20. https://doi.org/10.3389/fnagi.2021.617588

Moreno-Gonzalez, I., & Soto, C. (2011). Misfolded protein aggregates: Mechanisms, structures and potential for disease transmission. *Seminars in Cell and Developmental Biology*, *22*(5), 482–487. https://doi.org/10.1016/j.semcdb.2011.04.002

Nguyen, L. D., Chau, R. K., & Krichevsky, A. M. (2021). Small Molecule Drugs Targeting Non-Coding RNAs as Treatments for Alzheimer’s Disease and Related Dementias. *Genes 2021, Vol. 12, Page 2005, 12*(12), 2005. https://doi.org/10.3390/GENES12122005

Nilsson, P., Iwata, N., Muramatsu, S. ichi, Tjernberg, L. O., Winblad, B., & Saido, T. C. (2010). Gene therapy in Alzheimer's disease - potential for disease modification. *Journal of Cellular and Molecular Medicine*, *14*(4), 741–757. https://doi.org/10.1111/j.1582-4934.2010.01038.x

Ostadkarampour, M., & Putnins, E. E. (2021). Monoamine Oxidase Inhibitors: A Review of Their Anti-Inflammatory Therapeutic Potential and Mechanisms of Action. *Frontiers in Pharmacology*, *12*(April), 1–17. https://doi.org/10.3389/fphar.2021.676239

Pange, S. S., Patwekar, M., Patwekar, F., Alghamdi, S., Babalghith, A. O., Abdulaziz, O., Jawaid, T., Kamal, M., Tabassum, S., & Mallick, J. (2022). A Potential Notion on Alzheimer's Disease: Nanotechnology as an Alternative Solution. *Journal of Nanomaterials*, *2022*. https://doi.org/10.1155/2022/6910811

Pardo-Moreno, T., González-Acedo, A., Rivas-Domínguez, A., García-Morales, V., García-Cozar, F. J., Ramos-Rodríguez, J. J., & Melguizo-Rodríguez, L. (2022). Therapeutic Approach to Alzheimer’s Disease: Current Treatments and New Perspectives. *Pharmaceutics 2022, Vol. 14, Page 1117, 14*(6), 1117. https://doi.org/10.3390/PHARMACEUTICS14061117

Patwardhan, A. G., & Belemkar, S. (2021). An update on Alzheimer's disease: Immunotherapeutic agents, stem cell therapy and gene editing. In *Life Sciences* (Vol. 282). Elsevier Inc. https://doi.org/10.1016/j.lfs.2021.119790

Qiu, C., Kivipelto, M., & Von Strauss, E. (2022a). Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Https://Doi.Org/10.31887/DCNS.2009.11.2/Cqiu*, *11*(2), 111–128. https://doi.org/10.31887/DCNS.2009.11.2/CQIU

Qiu, C., Kivipelto, M., & Von Strauss, E. (2022b). Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention.

Https://Doi.Org/10.31887/DCNS.2009.11.2/Cqiu, *11*(2), 111–128. https://doi.org/10.31887/DCNS.2009.11.2/CQIU

Rajasekhar, K., & Govindaraju, T. (2018). Current progress, challenges and future prospects of diagnostic and therapeutic interventions in Alzheimer's disease. *RSC Advances*, *8*(42), 23780–23804. https://doi.org/10.1039/c8ra03620a

Reich, N., & Hölscher, C. (2022). *The neuroprotective effects of glucagon-like peptide 1 in Alzheimer ' s and Parkinson ' s disease : An in-depth review*. *August*. https://doi.org/10.3389/fnins.2022.970925

Rezaeian, A.-H., Wei, W., & Inuzuka, H. (2022). Review Regulation of neuronal autophagy and cell survival by MCL1 in Alzheimer's disease. *Acta Materia Medica 2022*, *1*(1), 42–55. https://doi.org/10.15212/AMM-2021-0002

Silva-Spínola, A., Baldeiras, I., Arrais, J. P., & Santana, I. (2022). The Road to Personalized Medicine in Alzheimer's Disease: The Use of Artificial Intelligence. *Biomedicines*, *10*(2). https://doi.org/10.3390/biomedicines10020315

Slevin, M., Matou, S., Zeinolabediny, Y., Corpas, R., Weston, R., Liu, D., Boras, E., Di Napoli, M., Petcu, E., Sarroca, S., Popa-Wagner, A., Love, S., Font, M. A., Potempa, L. A., Al-Baradie, R., Sanfeliu, C., Revilla, S., Badimon, L., & Krupinski, J. (2015). Monomeric C-reactive protein - A key molecule driving development of Alzheimer's disease associated with brain ischaemia? *Scientific Reports*, *5*(September), 1–21. https://doi.org/10.1038/srep13281

Sudhakar, V., & Richardson, & R. M. (2018). *Gene therapy for Neurodegenerative Diseases*. https://doi.org/10.1007/s13311-018-00694-0

Taoufik, E., Kouroupi, G., Zygogianni, O., & Matsas, R. (2018). Synaptic dysfunction in neurodegenerative and neurodevelopmental diseases: An overview of induced pluripotent stem-cell-based disease models. *Open Biology*, *8*(9). https://doi.org/10.1098/rsob.180138

Theleritis, C. G., Siarkos, K. T., & Politis, A. M. (2019). Unmet needs in pharmacological treatment of apathy in Alzheimer's disease: A systematic review. *Frontiers in*

Pharmacology, *10*(October). https://doi.org/10.3389/fphar.2019.01108

Trifunovic, D., Carvalho, L., Ilina, A., Khavinson, V., Linkova, N., & Petukhov, M. (2022). *Neuroepigenetic Mechanisms of Action of Ultrashort Peptides in Alzheimer's Disease*. https://doi.org/10.3390/ijms23084259

Tuszynski, M. H., Yang, J. H., Barba, D., Hoi-Sang, U., Bakay, R. A. E., Pay, M. M., Masliah, E., Conner, J. M., Kobalka, P., Roy, S., & Nagahara, A. H. (2015). Nerve growth factor gene therapy activation of neuronal responses in Alzheimer disease. *JAMA Neurology*, *72*(10), 1139–1147. https://doi.org/10.1001/jamaneurol.2015.1807

Vaz, M., Silva, V., Monteiro, C., & Silvestre, S. (2022). Role of Aducanumab in the Treatment of Alzheimer's Disease: Challenges and Opportunities. *Clinical Interventions in Aging*, *17*, 797. https://doi.org/10.2147/CIA.S325026

Wang, J., Yu, J. T., Tan, M. S., Jiang, T., & Tan, L. (2013). Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy. *Ageing Research Reviews*, *12*(4), 1024–1041. https://doi.org/10.1016/j.arr.2013.05.003

Wang, Q.-L., Chang-Le Fang, |, Xue, |, Huang, Y., & Xue, L.-L. (2022). *Research progress of the CXCR4 mechanism in Alzheimer's disease*. https://doi.org/10.1002/ibra.12026

Wilkinson, D. G., Francis, P. T., Schwam, E., & Payne-Parrish, J. (2004). Cholinesterase inhibitors used in the treatment of Alzheimer's disease: The relationship between pharmacological effects and clinical efficacy. *Drugs and Aging*, *21*(7), 453–478. https://doi.org/10.2165/00002512-200421070-00004

Xie, B., Tao, C., Li, J., Hilsabeck, R. C., & Aguirre, A. (2020). Artificial intelligence for caregivers of persons with Alzheimer's disease and related dementias: Systematic literature review. *JMIR Medical Informatics*, *8*(8). https://doi.org/10.2196/18189

Xie, H., Wen, H., Qin, M., Xia, J., Zhang, D., Liu, L., Liu, B., Liu, Q., Jin, Q., & Chen, X. (2016). In silico drug repositioning for the treatment of Alzheimer's disease using molecular docking and gene expression data. *RSC Advances*, *6*(100), 98080–98090. https://doi.org/10.1039/c6ra21941a

Xue, H., Li, J., Xie, H., & Wang, Y. (2018). Review of Drug Repositioning Approaches and Resources. *Int. J. Biol. Sci*, *14*(10), 1232–1244. https://doi.org/10.7150/ijbs.24612

Yefroyev, D. A. ;, Jin, S., Yefroyev, D. A., & Jin, S. (2022). *Citation: Induced Pluripotent Stem Cells for Treatment of Alzheimer's and Parkinson's Diseases*. https://doi.org/10.3390/biomedicines10020208

Zeng, Q., Siu, W., Li, L., Jin, Y., Liang, S., Cao, M., Ma, M., & Wu, Z. (2019). Autophagy in Alzheimer's disease and promising modulatory effects of herbal medicine. *Experimental Gerontology*, *119*, 100–110. https://doi.org/10.1016/J.EXGER.2019.01.027

Zhang, S., Zhang, M., Cai, F., & Song, W. (2013). Biological function of Presenilin and its role in AD pathogenesis. *Translational Neurodegeneration*, *2*(1), 1–13. https://doi.org/10.1186/2047-9158-2-15