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GENETIC INTERVENTION AND ALZHEIMER'S DISEASE: DAZZLING NEW DAWNS ON ALZHEIMER'S HORIZON

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UNDER THE GUIDANCE OF

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Genetic Intervention and Alzheimer's disease:

Dazzling New Dawns on Alzheimer's Horizon

A Thesis submitted to the Institute of Pharmacy, Nirma University, in partial fulfilment of the requirements for the Degree of

BACHELOR OF PHARMACY

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DECLARATION

We, **ABHISHEK GANATRA (20BPH002), DHRUV SUTHAR (20BPH026), DIPANGI PRAJAPATI (20BPH030), GAURAVSINH ZALA (20BPH033)** hereby declare that B.Pharm project work (BP812PW) entitled **"GENETIC INTERVENTION AND ALZHEIMER'S DISEASE: DAZZLING NEW DAWNS ON ALZHEIMER'S HORIZON"** being submitted to Institute of Pharmacy, Nirma University for the award of degree of B.Pharm was carried by us under the supervision of **Dr. Richa Gupta**, Institute of Pharmacy, Nirma University. The content of this project work, in full or in parts, has not been submitted to any other University for the award of any degree. We also declare that all the information collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.

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CERTIFICATE FOR SIMILARITY OF WORK

This is to undertake that the B.Pharm Project work (BP812PW) entitled **"GENETIC INTERVENTION AND ALZHEIMER'S DISEASE: DAZZLING NEW DAWNS ON ALZHEIMER'S HORIZON"** Submitted by **ABHISHEK GANATRA (20BPH002), DHRUV SUTHAR (20BPH026), DIPANGI PRAJAPATI (20BPH030), GAURAVSINH ZALA (20BPH033),** B.Pharm. Semester VIII is a Bonafide research work carried out by us at the Institute of Pharmacy, Nirma University under the guidance of Dr. Richa Gupta. We are aware about the rules and regulations of the Plagiarism policy of Nirma University, Ahmedabad.

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CERTIFICATE

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Abbreviations

1. AD - Alzheimer's disease
2. WHO - World Health Organisation
3. GDO - Global Dementia Observatory
4. DNA - Deoxyribonucleic acid
5. APP - Amyloid Precursor Protein
6. PSEN 1 - Presenilin 1
7. PSEN 2 - Presenilin 2
8. APOE - Apolipoprotein E
9. CSF - Cerebrospinal Fluid
10. MRI - Magnetic resonance imaging
11. FDA - Food and Drug Administration
12. PET - Positron emission tomography
13. BMT - Bone marrow transplant
14. SCID - Severe Combined Immunodeficiency
15. HSCT - Haematopoietic stem cell transplantation
16. Hct - Hematocrit test
17. EU - European Union
18. Aβ - Amyloid beta peptide
19. AAV - Adeno-associated viruses
20. scFv - Single-Chain Fragment Variable
21. TAU - Tubulin associated unit
22. MAPT - Microtubule Associated Protein Tau
23. RNA - Ribonucleic acid
24. BACE1 - beta-site APP-cleaving enzyme 1

25. NGF - Nerve growth factor
26. BDNF - Brain Derived Neurotrophic Factor
27. TrkB - Tropomyosin receptor kinase B
28. CREB - cAMP-response element binding protein
29. MRI - Magnetic resonance imaging
30. CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats
31. FAD - familial AD
32. SAD - sporadic AD
33. NMDA - N-methyl-D-aspartate
34. FDA - Food and Drug Administration
35. MCI - Mild cognitive impairment
36. IHME- Institute for Health Metrics and Evaluation

Abstract

Alzheimer's disease, a prevalent neurological condition that fallouts the memory loss and progressive cognitive impairments is one of the incurable conditions globally. The progression of the diseases increasing like anything as life expectancy increases, affecting millions of individuals globally, not limiting to the elderly but also to young onset day by day. Alzheimer's disease is one of the leading causes of dementia, accounting for 60-70% of all cases. According to estimates, it affects 5-8% of people over the age of 65 worldwide, and its prevalence upsurges significantly with age. Alzheimer's disease, the commonest type of dementia, is estimated to impact 50 million people worldwide, according to the World Health Organization. This amount is predicted to increase to more than 82 million by 2030 and more than 152 million by 2050, posing significant challenges for global healthcare systems. Memantine and cholinesterase inhibitors, as donepezil and related classes of the drug, are two often prescribed drugs that target neurotransmitters associated with memory and cognitive functions. While these therapies only lessen symptoms, they do not change the disease progression. Cognitive stimulation therapy and physical exercise are non-pharmacological therapies that enhance cognitive performance. There is an immediate need for neuron resilient rather than biological fires due to the alarming frequency and prevalence of Alzheimer's disease. The underlying genetic reasons of Alzheimer's disease can be addressed through the use of genome editing technologies like CRISPR/Cas9, which may eventually lead to more potent therapies or perhaps a cure. The current review has been carried out to unfold the covering of genomic modulation identifying the various gene therapies available and the potential of related technologies in tackling the global burden of Alzheimer's disease.

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Chapter 1 Introduction

The state known as dementia can be brought on by a variety of illnesses that gradually deteriorate brain tissue and kill nerve cells, impairing cognitive function (the capacity to think critically) more than would be predicted from the normal ageing process. AD is one of the most prevalent neurodegenerative diseases that is marked by progressive behavioral abnormalities, memory loss, and cognitive decline. The impairment of cognitive function does not alter awareness, but mood, emotional regulation, behaviour, and motivation are frequently affected along with or even ahead of the impairment. Dementia affects afflicted individuals as well as caregivers, families, and society at large on a social, psychological, physical, and economical level. Lack of knowledge and education about dementia is a significant obstacle to diagnosis and treatment since it fosters stigma.

According to World Health Organization projections, the number of dementia sufferers globally would rise from 55 million in 2019 to 139 million by 2050 as our society ages. By 2030, the estimated annual costs related to dementia are predicted to increase by almost 100%, from US$1.3 trillion in 2019 to $2.8 trillion. In 2019 there were 57·4 million cases of dementia worldwide; by 2050, predictions state that there would be 152·8 million cases. From 2019 to 2050, age-standardized both-sex prevalence did not vary much, despite significant increases in the estimated number of persons with dementia. In the world, estimates state that in 2019 the researchers anticipate that this trend will hold true until 2050. The estimated prevalence of dementia in persons 60 years of age and beyond in India is 7.4%; there are notable variations across states, in terms of sex, age and education gradients, and urban/rural divides. 8.8 million Indians over 60 are thought to be suffering from dementia. Different levels of local planning and support may be needed because the burden of dementia cases varies throughout states and subpopulations. Approximately 7 million people in America suffer from Alzheimer's disease. An estimated 6.9 million Americans 65 and older will develop Alzheimer's by 2024. 73% of the

population is 75 years of age or older. One in nine people who are 65 years of age or older suffer from Alzheimer's. More over two thirds of Alzheimer's patients in the United States are women. Older Black Americans are about twice as likely to get dementias such as Alzheimer's as older White people. The number of Americans 65 and older will increase, as will the percentage of the population with Alzheimer's or other dementias. (Lee et al.174-191)

Alzheimer disease (AD) is a neurological condition that progresses irreversibly. For the most part, current treatments simply address symptoms. In order to treat AD, we present here innovative treatments, including repositioned medications, as well as currently available commercial pharmaceuticals. Treatments aimed at the characteristics of AD are not very effective, despite great efforts. As per the US Food and Drug Administration (FDA), four distinct medications have been authorized for the management of AD: memantine in 2003, galantamine in 2001, rivastigmine in 2000, and donepezil in 1997. Nevertheless, there is no connection between these medications and the underlying pathology of AD. The only disease-modifying therapy (DMT) for the treatment of AD is audatenumab, a monoclonal antibody that the US FDA authorized in June 2021. Amyloid-β (Aβ) plaques and neurofibrillary tangles are the targets of this medication's design. Because effective pathogenic targets are unclear and early treatment of AD is crucial, there remain numerous challenges to be addressed in the understanding and treatment of AD. (Poudel and Park et al.)

The burden of AD is increasing due to aging populations, which emphasizes the need for efficient therapeutic interventions. Conventional pharmacotherapies, in spite of much research, control symptoms but do not alter the underlying progression of the disease. Looking into the aspects of current treatment availability regarding the AD, even with such a huge research into the area, Gene therapy emerges as a promising approach, offering targeted intervention at the molecular level. Gene therapy has a number of benefits over conventional pharmacotherapies. Through direct

delivery of therapeutic genes to specific cells, gene therapy facilitates the accurate manipulation of molecular pathways linked to the pathogenesis of disease. Additionally, gene therapy has the potential to produce long-lasting therapeutic effects, eliminating the requirement for frequent doses associated with traditional medications. Furthermore, platforms for gene therapy can be customized to increase specificity and reduce off-target effects, thereby enhancing treatment safety profiles. One illustrative example of successful gene therapy is the treatment of severe combined immunodeficiency (SCID), a hereditary condition potentially fatal characterized by profound immune system dysfunction. In SCID, mutations in genes encoding critical components of the immune system, such as the interleukin-2 receptor gamma chain (IL2RG) gene, result in impaired immune cell development and function. Beyond SCID, gene therapy holds promise for treating a myriad of inherited genetic diseases, including hemophilia, cystic fibrosis, and muscular dystrophy. For instance, in the case of hemophilia, which is caused by mutations in genes encoding clotting factors, gene therapy aims to introduce functional copies of these genes into target cells, thereby restoring normal clotting function and reducing the risk of spontaneous bleeding episodes.

Although preclinical research indicates that gene therapy for AD is feasible, there are significant obstacles in the way of implementing these results in clinical settings. Clinical trial design should give careful consideration to safety concerns such as vector-mediated toxicities, immune responses, and off-target effects. Optimizing gene delivery techniques to achieve adequate brain penetration and target cell specificity continues to be a significant challenge. Regardless of these obstacles, ongoing clinical trials are a promising means of assessing the safety regarding the efficiency of gene therapy strategies in individuals with AD.

The development of CRISPR-Cas9 and other gene editing technologies provides new opportunities for precise gene manipulation. Subsequent investigations should concentrate on optimizing gene delivery systems, enhancing therapeutic gene expression, and pinpointing innovative targets

for intervention. For gene therapy to be used in the treatment of AD more quickly from bench to bedside, cooperation between regulatory bodies, industry, and academia is crucial. In summary, gene therapy is a therapeutic modality that holds great promise for improving patient outcomes and quality of life. It has the potential to completely transform the way Alzheimer's disease is managed. (Raikwar, Sudhanshu P et al. 321)

With such a global prevalence and increasing incidences of Alzheimer's disease with no successful treatment, the current review study has been designed to look into the most recent developments in Alzheimer's care as well as the treatments that are now being offered. Our goal was to compile information regarding most immerging methods treatments as genome editing methods, their current implications and contribution to improving Alzheimer's disease, and their potential for curing the Alzheimer's disease. We in our review particularly targeted the CRISPR/Cas9 gene editing technique, a widely used technique now a day in basic and translational research, as a therapeutic entity for the treatment of the disease pertaining to the potential future entity in identifying a permanent cure for Alzheimer's. We had further extended the study by conducting survey looking for the awareness about Alzheimer’s disease in general population and awareness about the gene editing technique in the targeted research group.

Chapter 2 Literature Review

2.1 Alzheimer’s Disease and Global Prevalence

Alzheimer's disease is a relentless brain disorder that progressively robs individuals of their memories and thinking skills. Unlike the forgetfulness sometimes associated with aging, Alzheimer's is a thief that steadily dismantles cognitive abilities. As the most common cause of dementia, a condition marked by declining thinking skills, Alzheimer's significantly impacts daily life. Though it strikes most frequently after age 65, it's crucial to remember that Alzheimer's is not simply a consequence of getting older. This progressive disease dismantles a person's ability to function, posing immense challenges for patients and their caregivers.

An enormous and growing burden on health care has resulted from Alzheimer's disease (AD), a neurodegenerative illness that progress slowly. Because of aging populations and rising life expectancy, about 50 million people globally suffer from disruptive cognitive processes, and the number of newly diagnosed cases is rising quickly. As of 2019, official death certificates showed 121,499 fatalities from AD, making it the sixth most common cause of death in the US. Current estimates indicate that by 2050, there will be 12.7 million persons over 65 with Alzheimer's disease. As the population ages, it is anticipated that the entire cost of treating and caring for AD patients in 2020 will exceed $1 trillion, with an estimate of $305 billion.

The WHO states that dementia is an issue for public health. In May 2017, the World Health Assembly endorsed the global action plan for the public health response to dementia 2017–2025. Policymakers, as well as international, regional, and national partners, and the World Health Organisation, can utilise the Plan as a comprehensive guide for action in the following areas: dementia as a public health priority; dementia awareness and the creation of a dementia-inclusive society; dementia risk reduction; diagnosis, treatment, and care; dementia information systems; dementia carers' support; and research and innovation.

The World Health Organisation created an observatory for dementia globally, a database that gathers country information on 35 key dementia indicators throughout the global action plan's seven priority areas, to aid in the monitoring of the global dementia action plan. To support global action, WHO established the GDO Knowledge Exchange Platform, a repository of dementia-related best practices, to supplement the GDO. The platform aims to promote reciprocal learning and multidirectional exchange between nations, regions, and individuals.
(Greenblat et al. 432)

2.1.1 Etiology of Alzheimer's Disease

Alzheimer's is brought on by an aberrant accumulation of proteins in the brain. Degeneration of brain cells is caused by an accumulation of tau and amyloid proteins. The human brain is made up of over 100 billion neurons as well as several cell types. To perform all of the communications required for processes like learning, thinking, remembering, and planning, neural cells collaborate. Larger concentrations of amyloid protein called plaques are thought to accumulate within your brain cells by scientists. Tangles are caused by tau, a different protein, which has twisted filaments. Neurons ability to function is hampered by these plaques and tangles, which stop them from communicating with one another. Neural cells gradually and continuously die, which causes the symptoms of Alzheimer's disease. Neuronal cell loss frequently starts in the hippocampus, the part of the brain that controls memory, and then extends to other areas of the brain. Experts have been studying the exact cause of the accumulation of these proteins for years, but they are still unsure. Currently, an early onset genetic mutation is the most plausible theory for Alzheimer's disease. In the view, late-onset Alzheimer's disease results from a convoluted series of brain changes that can take decades to show symptoms. Hereditary, environmental, and lifestyle factors are likely to interact to determine the aetiology.

2.1.2 Current Diagnosis of Alzheimer's Disease

Alongside a thorough neurologic as well as mental state evaluation, a comprehensive history is necessary for the diagnosis of AD. A rigorous neuropsychiatric evaluation could occasionally be required in order to measure cognition precisely. Three organisations have established parameters for the diagnosis of AD: the Alzheimer Disease and Related Disorders Association, the National Institute of Neurologic and Communicative Disorders, and stroke. A diagnosis of probable Alzheimer's disease (AD) is made when there is no underlying systemic illness that could account for the condition, dementia and abnormalities in two or more cognitive domains, gradual cognitive worsening, and onset between 40 and 90 years of age. Additional favourable characteristics include a positive family history, normal CSF fluid examination results, normal results from brain MRI and electroencephalography, and normal outcomes. If a patient shows abrupt onset of memory issues early in the disease, gait abnormalities, seizures, or focal neurologic indications, another diagnosis has to be considered. According to the previously specified criteria, neuropathologic confirmation of the AD diagnosis was obtained in up to 90% of cases. (Handen et al. 173)

2.1.3 Treatment and Advancement throughout the various stages of Alzheimer's Disease

For the treatment of mild to moderate AD symptoms, three FDA-approved medications are available. The medications are not curative and cannot stop the disease from getting worse over time, even though they may slow down memory loss and lessen confusion. Indeed, following the administration of these medications, patients and their family frequently report no change in memory. The cholinesterase inhibitors, a class of medications that increase acetylcholine levels in the brain, include three medications used to treat AD: Ribastigmine, Donepezil and Galantamine. Due to specific side effects, many people might not be able to take AD medication. Galactonectin,

rivastigmine, and donepezil can cause nausea and difficulty swallowing. These drugs should only be taken by people with mild forms of AD, as the FDA has quickly approved both of them Lecanemab and Aucanumab. The goal of these drugs is to eradicate brain amyloid, one of the proteins that builds up in AD sufferers' brains. Before recommending these drugs, your doctor has to confirm whether amyloid is present in your brain. Your doctor will recommend either a spinal tap or an amyloid PET scan. Studies on aducanumab and lecanemab in people with early AD are still ongoing. The only medication that the FDA has licenced to treat symptoms associated with moderate to severe stages of AD is memantine (Namenda®). Memantine functions by lowering the brain's concentration of the neurotransmitter glutamate. It can be used with a cholinesterase inhibitor or without one. Menthol may cause headaches and dizziness as side effects.

Reference	Drug	Trial phase	Therapeutic target	Patients	Clinical trial number	Therapeutic effects	Safety	Side effects
Lenz et al. (2015)	ABT-089	2	α4β2 neuronal nicotinic receptor	Mild to moderate AD	NCT00555204	Lack of efficacy	Safe and well-tolerated	No data available
Gault et al. (2016), Florian et al. (2016)	ABT-126 (nelonicline)	2	α7 nicotinic receptor	Mild to moderate AD	NCT01527916; NCT01549834; NCT01676935	Lack of efficacy	Safe and well-tolerated	Agitation, constipation, diarrhea, fall and headache
Lacosta et al. (2018)	ABvac40	1	C-terminal of Aβ40	Mild to moderate AD	NCT03113812	Anti-Aβ40 antibodies production	Safe and well-tolerated	No data available
Timmers et al. (2018)	Atabecestat	1	BACE-1	Mild AD	NCT01978548; NCT02360657	Aβ reduction in CSF	Safe and well-tolerated	No data available
Logovinsky et al. (2016)	BAN2401	1	Aβ protofibril	Mild to moderate AD	NCT01230853	Plasma Aβ1-40 increase	Safe and well-tolerated	No data available
Brody et al. (2016), Salloway et al. (2018)	Bapineuzumab	2	N-terminus of Aβ	Mild to moderate AD	NCT01254773; NCT00606476	Lack of efficacy	Safe and well-tolerated	Cataract, injection site hemorrhage, nasopharyngitis, pneumonia and muscle twitching
Vandenberghe et al. (2016), Ivanoiu et al. (2016) Salloway et al. (2018)	Bapineuzumab	3	N-terminus of Aβ	Mild to moderate AD and prodromal AD	NCT00667810; NCT00996918; NCT00676143; NCT00937352; NCT00998764	Lack of efficacy	Safe and well-tolerated	Cataract, injection site hemorrhage, nasopharyngitis, pneumonia and muscle twitching
Arai et al. (2016)	Bapineuzumab	1	N-terminus of Aβ	Mild to moderate AD	NCT00397891	No results	Safe and well-tolerated	No data available
Fröhlich et al. (2019)	BI 409306	2	Phosphodiesterase type 9	Mild AD	NCT02240693; NCT02337907	Lack of efficacy	Safe and well-tolerated	No data available
Farlow et al. (2019)	Bryostatin	2	PKC epsilon activator	Advanced AD	NTRP101-202	Cognitive improvement	Safe and well-tolerated in low doses	No data available
Butchart et al. (2015)	Etanercept	2	TNF-α	Mild to moderate AD	NCT01068353	Lack of efficacy	Safe and well-tolerated	No data available
Ostrowitzi et al. (2017)	Gantenerumab	3	N-terminal and central amino acids of Aβ	Prodromal AD	NCT01224106	Lack of efficacy	Safe and well-tolerated	No data available
Rosenbloom et al. (2021)	Glulisina	2	Insulin	Mild and prodromal AD	NCT02503501	Lack of efficacy	Safe and well-tolerated	No data available
Bakker et al. (2021)	HTL0018318	1	M1 receptor	Healthy elderly and adults	NCT03456349	No results	Safe and well-tolerated	No data available
Atri et al. (2018)	Idalopirdine	3	5-HT6 receptor	Mild to moderate AD	NCT01955161; NCT02006641; NCT02006654	Lack of efficacy	Safe and well-tolerated	No data available
Relkin et al. (2017)	Intravenous immunoglobulin (IVIg)	3	Aβ	Mild to moderate AD	NCT00818662	Lack of efficacy	Safe and well-tolerated	No data available
Sakamoto et al. (2017)	Lanabecestat	1	BACE-1	Mild AD	NCT02005211	Aβ reduction in CSF and plasma	Safe and well-tolerated	No data available
Gauthier et al. (2016), Wilcock et al. (2018)	Leuco-methylthioninium bis (LMTM)	3	Tau	Mild to moderate AD	NCT01689246; NCT01689233	Lack of efficacy	Toxicity	Diarrhea, dysuria and decreased hemoglobin
Chen et al. (2022)	MLC901 (Neuroaid II)	2	ATP-sensitive potassium channels	Mild to moderate AD	NCT03038035	Potential decrease of AD progression	Safe and well-tolerated	No data available
Lawlor et al. (2018)	Nilvadipine	3	Calcium channel blocker	Mild to moderate AD	NCT02017340	Lack of efficacy	Safe and well-tolerated	No data available
Scheltens et al. (2018)	PQ912	2	Glutaminyl cyclase	Mild AD	NCT02389413	EEG frequency decrease and cognitive improvement	Toxicity	Nausea, diarrhea, constipation, infections, rash and urticaria
Moussa et al. (2017), Turner et al. (2015)	Resveratrol	2	SIRT1	Mild to moderate AD	NCT01504854	Attenuation of cognitive and functional decline	Safe and well-tolerated	Nausea and diarrhea
Fullerton et al. (2018)	SAM-760	2	5-HT6 receptor	Mild to moderate AD	NCT01712074	Lack of efficacy	Safe and well-tolerated	No data available
Nave et al. (2017)	Sembragiline	2	MAO-B	Moderate AD	NCT01677754	Only neuropsychiatric symptoms improvement	Safe and well-tolerated	No data available
Xiao et al. (2021)	Sodium oligomannate (GV-971)	3	Gut microbiota	Mild to moderate AD	NCT04520412	Cognitive improvement	Safe and well-tolerated	No data available
Liu-Seifert et al. (2018), Honig et al. (2018)	Solanezumab	3	Mid-domain of Aβ	Mild to moderate AD	NCT01900665	Lack of efficacy	Safe and well-tolerated	No data available
Decourt et al. (2017)	Thalidomide	2	TNF-α	Mild to moderate AD	NCT01094340	Lack of efficacy	Toxicity	Reduction in brain volume and neurological, urinary, gastrointestinal and skin adverse events
Pasquier et al. (2016), Van Dyck et al. (2016)	Vanutide cridificar (ACC-001)	2	N-terminal of Aβ1-7	Mild to moderate AD	NCT00479557; NCT00498602; NCT01227564	Lack of efficacy	Safe and well-tolerated	No data available
Egan et al. (2019)	Verubecestat	2	BACE-1	Prodromal AD	NCT01953601	Cognition and daily function decrease	Toxicity	Rash-related events, hair-color changes, falls, injuries, weight loss, and neuropsychiatric symptoms
Egan et al. (2018)	Verubecestat	3	BACE-1	Mild to moderate AD	NCT01739348	Lack of efficacy	Toxicity	No data available

Figure 2.1 Recent Advancements in treatment of AD

2.1.4 Genetics behind the Alzheimer's Disease

The majority of the time, multiple genes contribute to Alzheimer's. Rather, a multitude of genes together with environmental and lifestyle variables most likely impact it. A person's risk of contracting the disease may be raised or lowered by genetic variants, which are changes in the DNA. Over 80 genetic areas have been linked to Alzheimer's disease so far, according to scientists. It is currently known that just three of the genetic variations linked to Alzheimer's are causative of the illness. A person will probably get Alzheimer's before the age of 65, and occasionally much sooner, if they inherit a mutated version of one of these genes—APP, PSEN1, or PSEN2—even though this is rare. An escalated chance of Alzheimer's disease early in life is also seen in those with Down syndrome. A chromosome 21 extra that contains the APP gene, which makes the amyloid precursor protein, causes down syndrome. Brain beta-amyloid plaque accumulation is caused by an excess of this protein. In their 50s and 60s, the signs of Alzheimer's disease are expected to manifest in at least 50% of individuals with Down syndrome. There are several versions of the APOE gene, and it is known that one of these genetic variations affects the likelihood of developing Alzheimer's. In particular, for some groups, having APOE ε4 raises the risk of Alzheimer's and also contributes to the onset of the disease early. Potential defence against Alzheimer's disease may be offered by APOE ε2. The maturity of Alzheimer's disease is influenced by alterations in various genes as well as other biological, lifestyle, and environmental variables. Nevertheless, no one can predict with certainty whether a given person would get the illness.

2.2 Gene Therapy

Gene editing therapy is a novel approach to treating diseases by directly modifying the genes that cause them. Unlike traditional medications that just address symptoms, gene editing aims to provide a longer-term solution. It works by meticulously slicing and altering a specific DNA fragment that is present in a

cell. This might mean switching genes on and off, repairing a broken gene, or inserting a functional copy of a gene that is missing. Scientists utilize tools like CRISPR-Cas9, which acts as a molecular scissors, to make these changes. Many diseases, including cancer and genetic disorders like cystic fibrosis, may be cured using gene editing therapy. As it is still in its early stages, more study has to be done to ensure safety and efficacy before widespread usage.

2.2.1 Timeline of historical aspects of Gene therapy

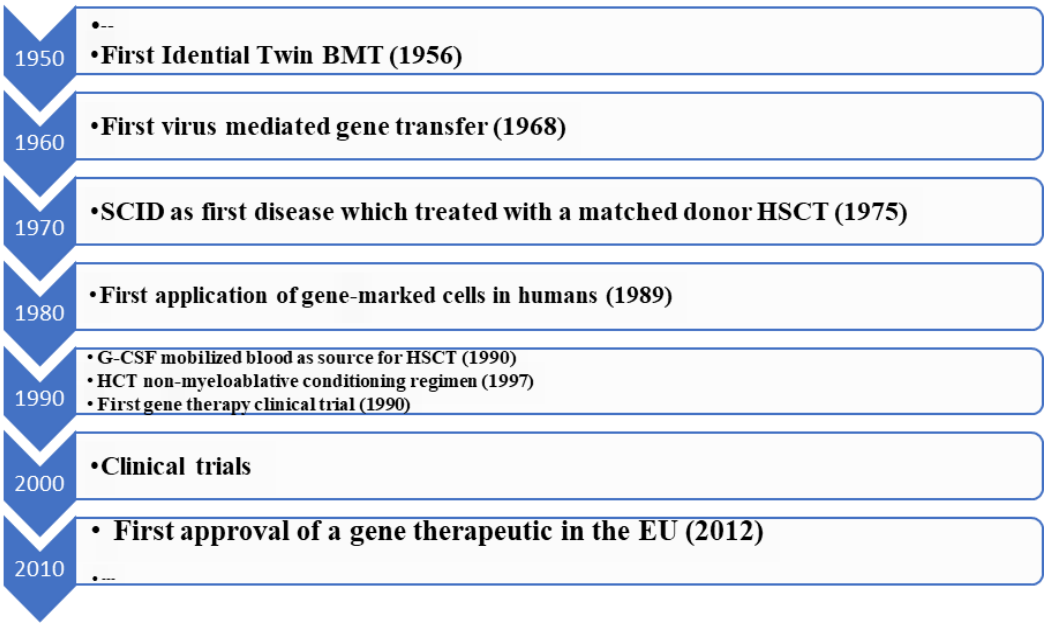

Figure 2.2: Timeline for Gene Therapy

2.2.2 Summary of Gene Therapy in AD: Molecules targeted

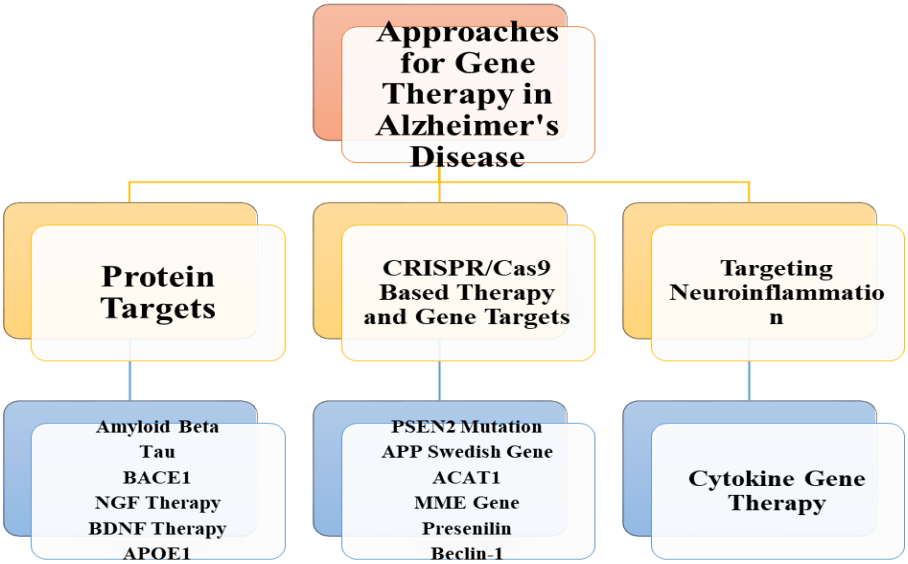

Figure 2.3 Summary of Gene Therapy in AD

2.2.3 Targeting Amyloid- B (AB)

Numerous studies have shown that amyloid plaques, which are created when the β- and γ-secretases sequentially cleave the amyloid-β protein precursor (AβPP), are the hallmark of AD. Aβ comes in a variety of forms, such as Aβ34, Aβ40, Aβ42, and so on. Aβ42, which is generated in smaller quantities and is crucial for Aβ accumulation in the brain, is the principal culprit despite Aβ40 being the most abundant physiological form. The pathogenesis of AD is initiated by an abnormal build-up of Aβ aggregates. With variable degrees of success, several attempts have been undertaken to obstruct this important pathogenic pathway. An important part of neurodegeneration and AD pathogenesis is autophagy. Pickford et al.'s research has shown that the autophagy related protein Beclin1 maintains the build-up of Aβ in mice and is reduced in early stage AD patients. An appealing strategy to improve AD pathogenesis is to target Aβ. Zhang et al. performed one of the first attempts, creating a recombinant AAV that expressed the fusion protein Aβ42 and the cholera toxin B component, known as CB-ABeta42. Using the intranasal, intramuscular, or oral methods, Anti Aβ42 antibody levels were raised in PDAPPV7171 transgenic mice following an injection of the AAV CB Aβ42 vaccine. Elevated anti-Aβ42 antibody levels resulted in a noteworthy decrease in the amount of Aβ in the brain, a reduction

in plaque-associated astrocytosis, and enhancements in cognitive and memory functions. Subsequently, Fukuchi et al. produced an AAV that expressed anti-Aβ single-chain antibody, which was injected into the corticohippocampal regions of Tg2576 mice. According to their findings, scFv was expressed continuously for a year without causing any neurotoxicity. The Tg2576 mice had less Aβ deposits in their brains, but no functional cognitive testing was done, which made it challenging to interpret the results. (Raikwar and Sudhanshu P et al. 321)

2.2.4 Targetting TAU

In the pathogenesis of AD and a number of other neurodegenerative diseases, Tau is essential. It is essential to target tau and Aβ at the same time in order to effectively treat AD. Many attempts have been made to use either gene silencing or anti-tau antibodies to eradicate the harmful tau forms. In order to develop a new tau knockout strain (tauΔex1), Tan et al. most recently reported employing CRISPR/Cas9-mediated genome editing of exon1 and intron 1 of the Mapt gene in C57Bl/6J mice. The transcriptional start codon is located 115 bp up and 18 bp downstream thanks to CRISPR/Cas9 genome editing. A modest deletion was introduced at the MAPT intron-1/exon1 junction using two guide RNAs. The two guide RNAs and the CRISPR/Cas9 protein were injected straight into the fertilized oocytes' cytoplasm. Tau–/–has traditionally been produced by targeting genes in ES cells, which has required the insertion of large selective marker cassettes into the MAPT coding area. This strategy's drawback is that these selectable markers might result in unpredictable and undesirable effects. These mice showed normal memory development in young mice and a dramatically lowered sensitivity to excitotic convulsions, even though they did not display the overt phenotype. Numerous Aβ-targeting immunotherapies were discontinued because of safety issues, the emergence of neurovascular side effects, and other unfavorable outcomes. As previously shown by Holtzman et al., passive vaccination with an anti-Tau antibody HJ8.5 decreases the accumulation of pathogenic tau in a human P301S tau-expressing transgenic (P301s-tg) mice model of

FTD/tauopathy. In an effort to enhance their findings even more, they created an AAV2/8 vector that expressed anti Tau scFv and proved that astrocytes and neurons both expressed anti-scFvs. While retaining their antigen binding specificity, these anti-Tau-scFvs were able to effectively reduce pathological tau build-up in the hippocampus regions of P301S-tg animals. These results demonstrate that AAV-mediated gene transfer might be used to deliver neurotrophic growth factors, microRNAs, CRISPR/Cas9, scFvs, or any conceivable combination of these agents therapeutically. (Raikwar and Sudhanshu P et al. 321)

2.2.5 Targeting BACE1

Overexpression of BACE1 plays a role in pathogenesis. Reduced cerebral Aβ levels can be achieved by targeting BACE1, an interesting AD therapeutic target that functions upstream of γ-secretase in amyloid processing. Many BACE1 inhibitors are now being researched for the treatment of AD. However, Merck & Co. recently made the decision to halt recruiting more than two thousand patients with mild to severe AD in a significant phase II/III study for Verubecestat, a BACE1 inhibitor. Moreover, there are a number of BACE1 inhibitor trials, including phase II/III trials of Johnson & Johnson's JNJ-54861911 for asymptomatic at-risk patients with family history, APOE4 or biomarker positivity, and phase II trial of Novartis' CNP520 for asymptomatic at-risk patients. Phase III trials for early AD using Biogen/Eisai's Elenbecestat are also available . A phage-derived human antibody with high affinity for BACE1 has been produced by Atwal et al. Both in vivo and in vitro BACE1 activity is inhibited by anti-BACE1 antibodies. When anti-BACE1 antibody was administered at doses of 30 and 100 mg/kg, Aβ1 - 40 and Aβ1 - 42 were reduced by 70% in five-month-old Tg2576 mice. When examined in the PS2APP mouse model, on the other hand, it revealed a decrease in peripheral Aβ but not in brain Aβ. (Raikwar, Sudhanshu P et al. 321)

2.2.6 NGF Therapy

AD is a very complicated neurological disease, and the majority of existing treatment approaches are ineffective, causing AD patients' cognitive abilities to gradually deteriorate. There exist several treatment targets that may be employed to impede or postpone the advancement of AD. Tuszynski et al. implanted autologous fibroblasts genetically engineered to express human NGF into the forebrain of eight patients with mild AD as part of a phase I study of ex vivo NGF gene transfer. These studies resulted in an improvement in the pace of cognitive decline without any detrimental long-term effects. Bishop et al. assessed the therapeutic potential of AAV2-NGF (CERE-110) for targeted, continuous, and persistent NGF administration and trophic action in mouse basal forebrain cholinergic neurons in an intriguing preclinical investigation. According to their research, NGF transgene delivery to the intended brain area is accurate, reliable, and results in long-term NGF production without protein loss or accumulation. Additionally, the findings showed that CERE-110 had bioactive effects on young rat basal forebrain cholinergic neurons and was both neuroprotective and neurorestorative to basal forebrain cholinergic neurons in the rat fimbria-fornix lesion and elderly rat models. A phase I gene therapy trial was initiated by Rafii et al. using these and other primatological studies, wherein individuals with AD were stereotactically injected with CERE-110 in the nucleus basalis of Meynert. The AAV2-NGF vector used in this work includes an expression cassette including the human growth hormone polyadenylation signal, human NGF cDNA, and the CAG promoter. Over a two-year period, the study showed that the technique was safe, tolerable, and caused the least amount of cognitive impairment. The effects were dose dependant. Neuropsychological tests and Positron Emission Tomography imaging did not show any signs of accelerated cognitive deterioration. Long-term, targeted, gene-mediated NGF expression and bioactivity were found during the brain autopsy. Future AAV-based gene therapy trials for AD and other neurodegenerative illnesses are now possible because to these phase 1 investigations. (Raikwar, Sudhanshu P et al. 321)

2.2.7 BDNF therapy

Since AD has been demonstrated to cause a reduction in BDNF levels, raising BDNF levels may help with AD therapy. Chen et al. investigated the effects of AAV-ProBDNF in APPswe/PS1dE9 mice. According to their findings, proBDNF worsens brain Aβ burden and exacerbates memory and learning impairment. These studies do not, however, clearly indicate how proBDNF exacerbates memory and learning deficits. Osborne et al. have developed a novel gene therapy vector to generate permanent BDNF activation in neurons. BDNF signaling is mediated by p75 and TrkB. Nonetheless, it has been demonstrated that overexpression of BDNF results in TrkB receptor downregulation.They have created a unique gene sequence that concurrently codes for the TrkB receptor and BDNF, with a brief viral-2A sequence separating them, in order to get around this restriction. Following the production of this new gene sequence using AAV, HEK293 and SH-SY5Y cells exhibited enhanced intracellular signaling mediated by BDNF and TrkB. Analyzing this vector's therapeutic effectiveness in vivo across a variety of AD models will be fascinating. Aβ deposition is known to interfere with the function of the cAMP-response element binding protein (CREB), as Caccamo et al. Furthermore, in the 3xTg-AD mouse model, lentiviral-mediated gene transfer of the CREB binding protein alleviated learning and memory impairments and raised BDNF levels. In an effort to cure AD and lessen neurodegeneration and related memory loss, Nagahara et al. most recently assessed the delivery of the BDNF gene to the entorhinal cortex [40]. MRI guided and convection enhanced distribution of AAV2-BDNF provided targeted delivery to the entorhinal cortex of non-human primates. (Raikwar and Sudhanshu P et al. 321)

2.3 Introduction to CRISPER

CRISPR, known as Clustered Regularly Interspaced Short Palindromic Repeats, is an advanced gene editing method. In Alzheimer's research, CRISPR is used to target and alter specific DNA sequences, offering potential benefits for studying and treating the disease by

addressing genetic factors linked to Alzheimer's. Effective gene editing tool Cas9, which is associated with CRISPR-related short palindromic repeats, recognizes a certain gene sequence and initiates a double-strand break that leads to either gene correction or inactivation. **(**Hanafy and Sayed et al. 175**)**

2.3.1 Timeline of CRISPR

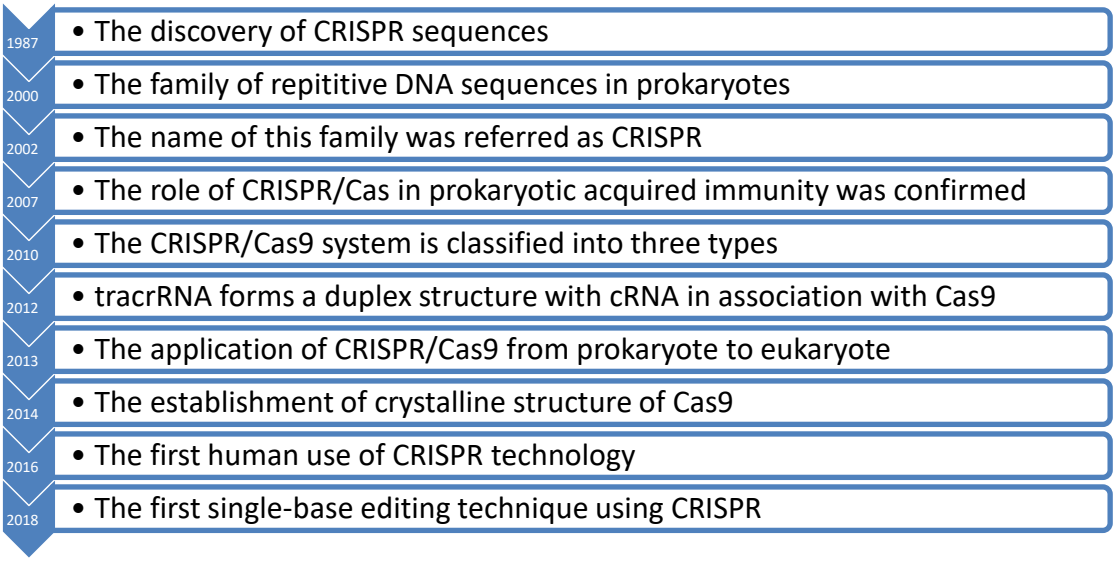

Figure 2.4: Timeline of CRISPR

AD models with early onset and sporadic onset can both benefit from the application of the CRISPR-Cas9 technology. Correcting mutations and introducing genetic elements to specific DNA areas in cells or tissues is possible using CRISPR, as it can successfully target any specific gene sequence. Improved cellular and molecular replicas, function knockout, investigation of lethal neuronal injury, disease model mimicking, and genome-insertion of guide gene sequence are all demonstrated by this tool's efficacy. Screening for relationships between risk polymorphisms and cellular pathways, specific pathways connected to pathogenesis, and phenotypic differences can all be done with CRISPR-Cas9. Adverse effects of CRISPR-Cas9 have been shown when it comes to correcting specific gene sequences. Numerous in vitro and in vivo trials have been conducted on it. (Barman et al.419-434)

2.3.2 Data available regarding CRISPR/ CAS9 gene editing technique

One component of prokaryotes' adaptive immunity is CRISPR/Cas9. A Cas9 nuclease and a CRISPR cassette make up this system. Prokaryotic cells are resistant to bacteriophages and plasmids containing protospacers, which are complementary to those found in a CRISPR cassette, when CRISPR cassettes and Cas are used together. By 2050, there will be over 131 million cases of dementia worldwide, accounting for a cost of over US$818 billion. Currently, over 46 million people suffer from dementia. About 1% of familial cases of AD are caused by genetic mutations; hence, CRISPR/Cas9 genome editing may be helpful in treating familial AD (FAD) in general, while having little to no effect on sporadic AD (SAD). However, reducing Aβ synthesis may offer a therapeutic approach regardless of the origin, whether familial or sporadic, given the relevance of dysregulated Aβ metabolism in FAD and SAD.

2.3.3 Current implications of CRSIPER in AD

As of right now, there is no medication therapy that completely cures AD. Numerous treatments and combination treatments have been discovered that have the potential to alleviate symptoms or reduce neuropathology. Cholinesterase inhibitors and NMDA receptor antagonists are the two main medication classes and combination therapies utilized to treat AD patients. As of 2020, 121 distinct treatments for Alzheimer's disease (AD) are enrolled in research trials, according to clinicaltrials.gov. Presumed to be disease-modifying drugs, the bulk of Alzheimer's disease treatments are intended to halt or delay the progression of the illness. Aduchelm, or Aducanumab: In June 2021, the FDA approved a monoclonal antibody for the treatment of AD using the "Accelerated approval pathway."

In 2023, two novel CRISPR-based Alzheimer's treatment strategies were presented online and at the Alzheimer's Association International Conference (AAIC), which was held in Amsterdam, Netherlands. One is to lessen the influence of APOE-e4, the strongest known gene associated with Alzheimer's disease. The other seeks to reduce the amount of beta amyloid, a dangerous molecule that is a hallmark of Alzheimer's

disease and the target of recently authorized therapies, in the brain. Small Molecule Targeted Recruitment of a Nuclease to RNA in RNA Modification Tools. The emergence of CRISPR-Cas9 technology has been a major source of hope for bringing gene editing technologies into the clinic for safe and efficient application. (Aulston et al.)

2.3.4 Human Clinical Trials

To evaluate the safety and effectiveness of a gene therapy to deliver a critical protein into the brains of people with Alzheimer's disease (AD) or mild cognitive impairment (MCI), a condition that frequently precedes full-blown dementia, researchers at the University of California San Diego School of Medicine have initiated a first-in-human Phase I clinical trial. Twelve individuals with AD or MCI diagnoses will be enrolled in the three-year trial to receive AAV2-BDNF treatment, while the remaining twelve will serve as comparative controls. This is the first evaluation of AAV2-BDNF's safety and effectiveness in people. In a prior gene therapy experiment conducted between 2001 and 2012, participants' brains showed increased growth, axonal sprouting, and activation of functional indicators when AAV2 and a different protein known as nerve growth factor (NGF) were used. A plethora of clinical trials are being conducted to evaluate medicinal treatments. Gene therapy, which made its debut in 1980 and has been tested on a variety of illnesses and ailments, according to Tuszynski, represents a distinct approach to a sickness that calls for novel theories about the illness and novel therapeutic approaches. According to a 2022 study by Konstantinidis et al., the CRISPR-Cas9 method can partially restore the aberrant Aβ42/40 ratio that causes the disease to develop in carriers of this mutation and preferentially disrupt the PSEN1M146L allele responsible for AD. (LaFee et al.)

2.4 Economic cost of Alzheimer’s globally

Evaluating the entire economic impact of Alzheimer's disease is crucial, partly because it helps determine if the costs borne by health systems to diagnose and subsequently treat so many patients are reasonable. In order to achieve this, we have

thoroughly analysed data from numerous sources, historical studies, and the renowned Institute for Health Metrics and Evaluation (IHME), a research institution that specializes in calculating the worldwide burden of diseases. Our scientific methodology uses people's willingness to pay to reduce their risk of death to assess the economic cost of Alzheimer's disease. A macroeconomic model of an economy's productive capacity that takes into consideration the decline in labour and capital formation brought about by an increase in illness incidence has been developed. These approaches account for the whole economy as well as a wide range of direct and indirect costs associated with Alzheimer's disease for both patients and caregivers.

We project the disease's worldwide economic effect to be $2 trillion in 2019 using our willingness-to-pay methodology. That debt is expected to soar to roughly $10 trillion, and maybe as much as $13.5 trillion, by 2050. Conversely, projections indicate that the global GDP (adjusted for inflation) will reach $228 trillion by 2050. (Bloom et al.)

CHAPTER 3 Material and Method

3.1 Introduction to Chapter

This chapter goes into detail on the methodology utilized to carry out the article selection and analysis for relevantly selecting studies. Data interpretation and analysis were also addressed in this technique chapter. Among the discrete procedures that comprised the literature search for conducting the selected study were the problem documentation, literature search, and data processing.

For the selection of the studies, the most reliable and authentic databases were employed. These databases include a range of websites from periodicals, different online sources, to find studies published about the topic, search engines like MEDLINE and PubMed, Science Direct were utilized. In order to locate and search for the necessary information, searches on Google, numerous accessible websites, and numerous significant journals were conducted.

The phrase "Alzheimer's disease," "gene editing technique," "CRISPR/Cas9," and other variations are among the combinations found in the keyword search.

3.2 Part one: Review of literature

3.2.1 Literature search and article selection process

Thorough research begins with a well-crafted and thorough literature review and article selection. The impact of the study is particularly enhanced and

improved by a strong critical review. The study's utility is increased by thorough reviews. The different available sources were used to guide the systematic review. The studies pertaining to the prevalence and advances of Alzheimer's disease particularly gene editing were included in the search for articles. About thirty-five research articles were reviewed in the process. After a thorough analysis of the studies, certain publications that met the insertion criteria and in-depth reviews were chosen, and few important studies were ultimately included in the review study. The inclusion and exclusion standards for the literature search.

3.2.2 Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. The studies which were published in English 2. The studies which were published between 2010-2024 3. The articles focusing on Gene and related technologies were focused more.	1. The studies which were published other than in the English language 2. The Studies were published before 2010 or so on. 3. The articles other than details of gene therapy in AD were not included in the study.

Table 3.1: Inclusion and Exclusion Criteria

3.3 Part two: Survey Studies

The second part of the study includes the awareness survey about Alzheimer’s disease among general public and other to the targeted research group associated with Alzheimer’s and related studies for finding the awareness about gene editing and CRISPER technology in treatment of Alzheimer’s disease.

Participants selection and details:

Participants in our study includes from the local community as well as the university campus. The objective of this methodology was to obtain a thorough grasp of the attitudes and knowledge regarding Alzheimer's disease in both academic and general society settings. By including a variety of groups, we aimed to identify important areas for focused education and intervention as well as any awareness gaps. The results of this comprehensive survey will provide important new information for developing public health campaigns and outreach programs related to Alzheimer's disease education.

3.4 Survey Questionnaire

Prior to running our survey on the general public's and research researchers' awareness of Alzheimer's disease and latest advancement to gene therapy and CRISPER, the critical analysis was done to design the specific question for the both group. The quantitation of the selected studies was performed by incorporating numerous questions and related tools to identify the awareness, prevalence and advancement in the area of Alzheimer’s disease particularly targeting to the latest gene editing technology.

The basis of selection of questions was as follows below:

1. What is the baseline level of awareness about Alzheimer's among research scholars and the general public?

2. Are there differences in awareness levels between these two groups? If so, what factors might contribute to these differences?

3. How does awareness vary between participants on campus versus those off campus?

4. What are the common misconceptions or gaps in understanding regarding Alzheimer's disease within each group?

5. What resources or information channels are currently utilized by participants to learn about Alzheimer's?

6. What are the attitudes and perceptions towards Alzheimer's disease within

these distinct groups?

7. Are there particular demographics (age, education level, profession) that correlate with higher or lower levels of awareness about Alzheimer's?

8. What are the preferred formats or methods for receiving information about Alzheimer's among these groups?

9. How might the findings from this survey inform future awareness campaigns or educational initiatives about Alzheimer's disease?

10. What are the potential implications of improving Alzheimer's awareness within academic and community settings?

11. Whether the research scholars are familiar with the terms gene editing and CRISPR/ Cas9 gene editing technology?

12. What are the majority of resources they used to claim knowledge about these techniques?

13. How much potential they find in these techniques with respect to Alzheimer’s treatment and whether they feel there’s a light at the end of this tunnel or not?

14. Do they find these tools safe or suitable for Alzheimer’s treatment and whether the research works regarding CRISPR and gene therapy are receiving ample amounts of funds?

Our survey's design and analysis were influenced by these questions, which also helped us define the goals and expected results of our investigation.

Chapter 4 Result

4.1 Part one: Review of Literature

4.1.1 Literature search and Articles descriptions

Our linked research publications indicate that scientists are approaching Alzheimer's from several perspectives. One tactic aims to eliminate or prevent the production of protein culprits such as Tau tangles and Aβ plaques from the brain. By delivering genes for nerve growth factors (NGF and BDNF) to enhance neuron health, another strategy aims to strengthen the brain's natural defences. This multifaceted strategy is promising for the effective fight against Alzheimer's in the future. Studies indicate a promising path for treating Alzheimer's disease. Targeting both the brain's natural defences and the proteins causing the disease, a multifaceted strategy is being implemented. With the use of nerve growth factors, this method may be able to strengthen brain health by preventing or eliminating toxic protein accumulations. There is a great deal of hope for the future of Alzheimer's treatment because of these joint efforts. Our references state that CRISPR/Cas9 gene editing presents a ground-breaking method for treating Alzheimer's. Although information is still developing, it appears promising for perhaps modifying disease-associated genes such as APP, PSEN1, APOE4, and others. Reducing tau tangles and amyloid plaque accumulation could mitigate AD symptoms. Human studies are just getting started, but researchers are looking at using CRISPR to deliver these edits straight to brain cells. Though its safety and efficacy in treating Alzheimer's disease are still unknown, CRISPR offers hope for the day when the illness might be targeted at its genetic source. Thus, CRISPR/Cas9 genome editing appears to be a promising therapy strategy for Alzheimer's. According to preliminary findings, it may be possible to modify the genes linked to the illness and influence how aberrant proteins are formed in the brain. Although human trials are still in their early phases, CRISPR presents a fresh strategy for genetically targeting Alzheimer's disease.

4.2 Part two: Survey Questionnaire

4.1.2 Survey

Part 1: Common Audience comprising of 156 responses:

We polled 156 participants in this study to gauge their level of awareness of Alzheimer's disease according to different criteria. Questions about Alzheimer's symptoms, risk factors, prevention techniques, and potential therapies were included in our survey to see how well-informed individuals were. We also investigated their opinions regarding early diagnosis and identification as well as their acquaintance with assistance resources. To examine any potential disparities in awareness, we grouped individuals based on factors like age, education level, and region. According to our research, there is a need for focused education initiatives to improve public knowledge about Alzheimer's disease, particularly among particular demographic groups where awareness may be low. The important information gathered from this survey will help guide future initiatives to raise awareness of Alzheimer's disease and, eventually, enable better outcomes for those who are impacted by it. The interested findings of the individual part been summarized here as:

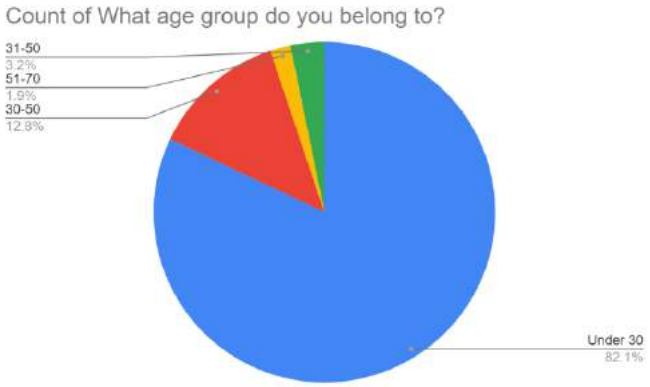

Figure 4.1: Age Group of Respondents

The pie chart shows that the vast majority of respondents, 82.1%, were under 30 years old. The remaining 17.9% of respondents were divided between two age groups: 31-50 (3.2%) and 50-65 (12.8%).

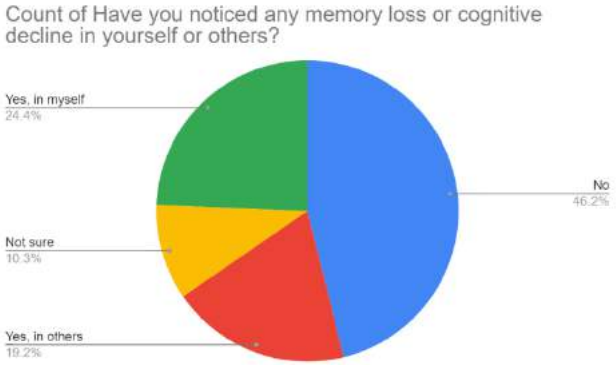

Figure 4.2: Respondents count of memory loss in themselves or others

Out of the 156 people surveyed, 46.2% said yes they had noticed memory loss or cognitive decline in themselves, 19.2% said yes they had noticed it in others, 24.4% said no, and 10.3% were not sure

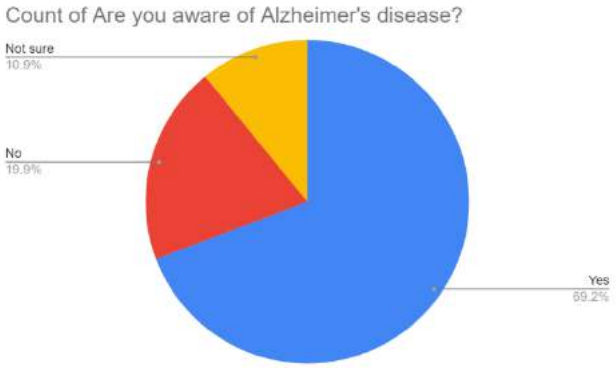

Figure 4.3: Awareness about Alzheimer's disease

This suggests that a majority of the respondents (69.2%) are not sure about Alzheimer's disease.

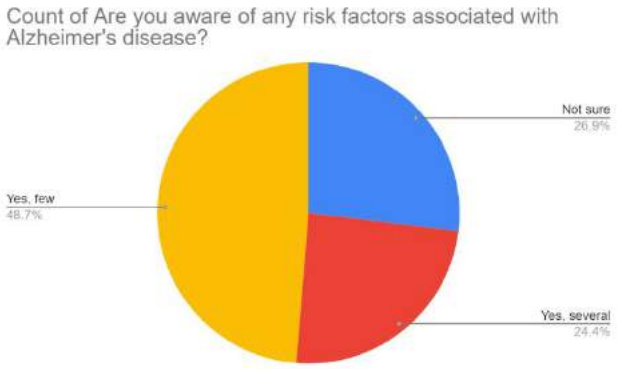

Figure 4.4: Awareness about any risk factors associated with Alzheimer's disease

The observation is that awareness of Alzheimer's disease risk factors is unevenly distributed among the 156 respondents.

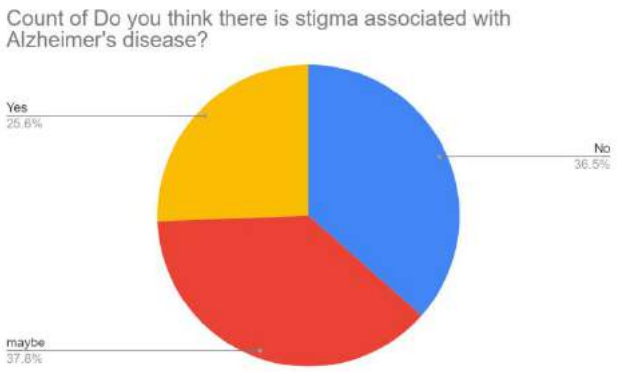

Figure 4.5: Count on stigma associated with Alzheimer's disease

Majority believes there's a stigma associated with Alzheimer's disease. This suggests that a significant portion of the population (37.8% + 36.5% = 74.3%) either believes there is a stigma or is unsure about it.

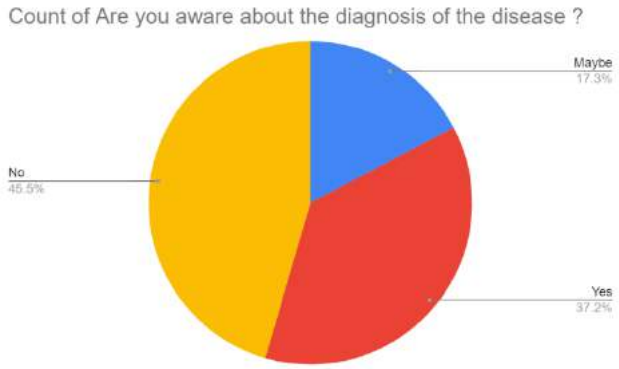

Figure 4.6: Awareness about the diagnosis of the disease

The observation is that awareness about the diagnosis of a disease is unevenly distributed among the 156 respondents.

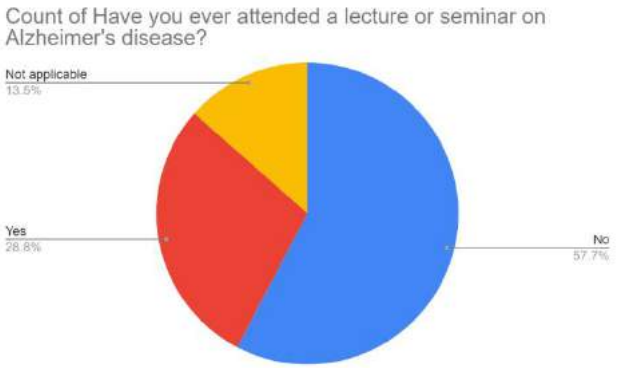

Figure 4.7: Count of attendees in any seminar or lecture related to Alzheimer's disease

The pie chart shows that whether they had ever attended a lecture or seminar on AD, most people (57.7%) had not. Majority of the people surveyed have not learned about AD through lectures or seminars.

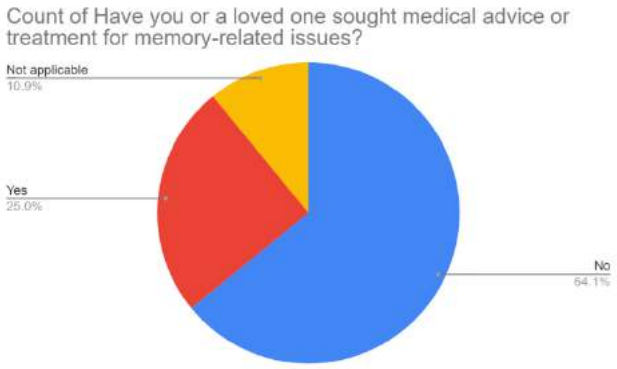

Figure 4.8: Count of Respondents who sought treatment for memory related issues

This pie chart suggests that a significant portion of the respondents (64.1%) have either sought medical advice or treatment for memory-related issues themselves or for someone they know.

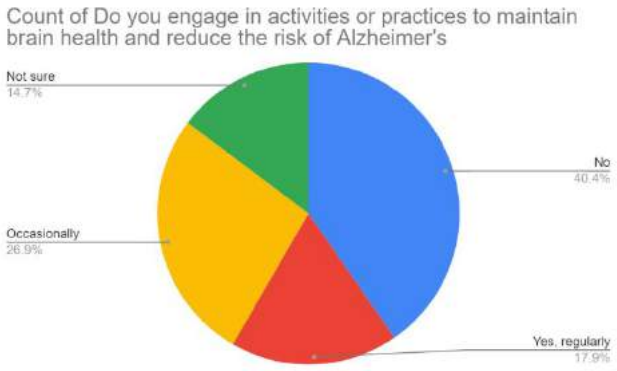

Figure 4.9: Engagement in activities to reduce risk of Alzheimer's disease

This pie chart suggests that over half of the respondents (40.4% + 17.9% = 58.3%) reported engaging in activities or practices either regularly or occasionally to maintain brain health and reduce the risk of AD.

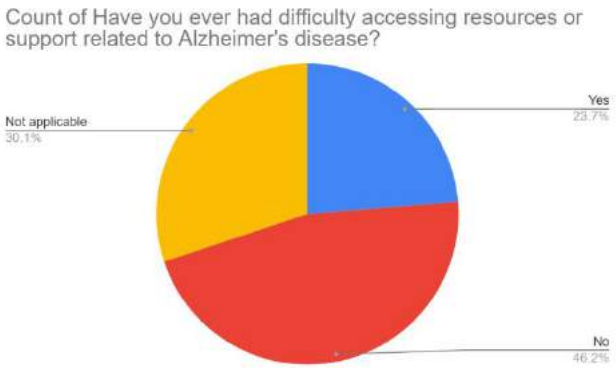

Figure 4.10: Count on Respondents who faced difficulties in accessing resources related to Alzheimer's disease

A significant portion of the respondents did not encounter difficulty finding Alzheimer's resources (46.3%, who said not applicable). However, a non-trivial portion (30.1%) did report difficulty finding resources or support.

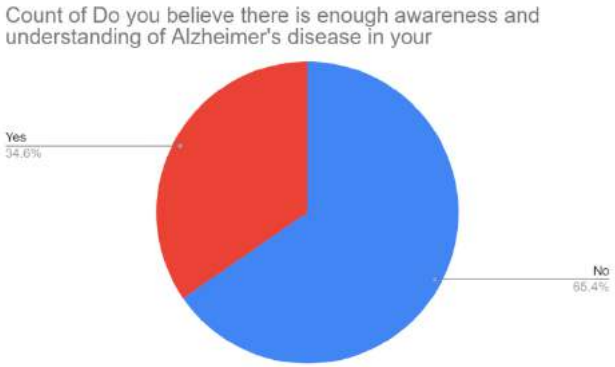

Figure 4.11: Respondents take on enough Awareness about Alzheimer's disease is available or not

This chart suggests, majority of respondents (65.4%) feel there is enough awareness and understanding of AD. However, a significant minority (34.6%) believes there isn’t enough awareness and understanding.

Part 2: Research Group comprising of 18 responses:

In order to learn more about the knowledge and attitudes of university research students about Alzheimer's disease awareness, including gene editing tools like CRISPR/Cas9, a group of research students was thoroughly polled. Because of their academic background, this group of students showed a better baseline understanding than the general public polled in related studies. The research team's findings demonstrated a more sophisticated comprehension of the pathophysiology of the disease, available therapeutic options, and cutting-edge tools like CRISPR/Cas9 for precise genetic editing in Alzheimer's research.

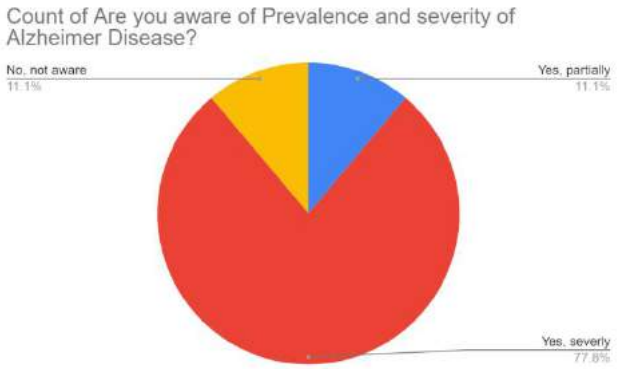

Figure 4.12: Awareness about Prevalence and severity of Alzheimer's disease

A very small percentage of people, 11.1%, are aware of the prevalence and severity of Alzheimer's disease. There is a large portion, 77.8%, who aren’t aware. This suggests that there is a need for increased awareness about it.

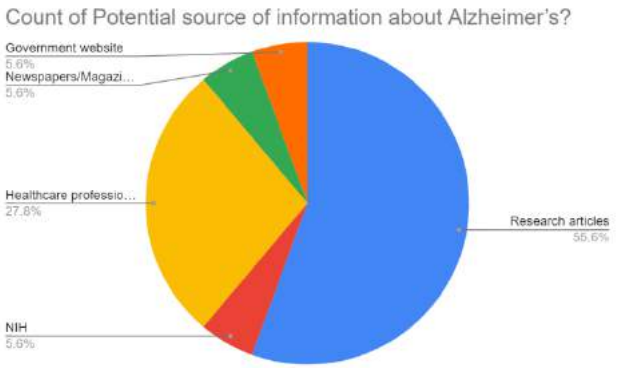

Figure 4.13: Potential source of Alzheimer's disease

Research articles are the most common source of information, at 55.6%. Newspapers, magazines and government sites account for 16.8%. Healthcare professionals and NIH each make up a small portion(5.6%).

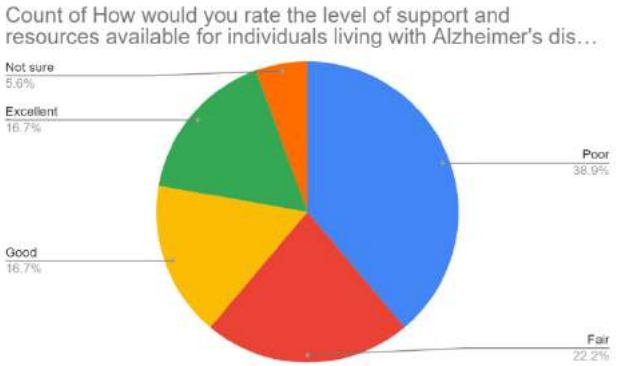

Figure 4.14: Respondents ratings on the level of support and resources available for individuals living with Alzheimer's disease

The level of support and resources available for individuals with Alzheimer's, is rated as fair by 22.2% of respondents. A larger portion, 38.9%, rated the level of support and resources as poor. 16.7% each rated the level as good or excellent, and 5.6% were unsure.

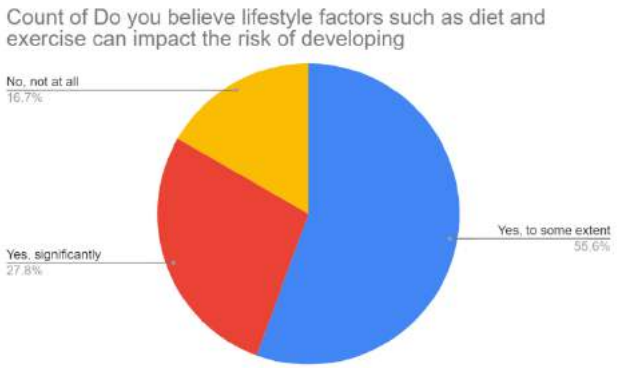

Figure 4.15: Life style factors affecting Alzheimer's disease

A majority of respondents, 83.4%, believe that diet and exercise can impact the risk of developing Alzheimer's disease. Only 16.7% of respondents disagreed. This suggests that most people are aware that diet and exercise are important factors in reducing the risk of AD.

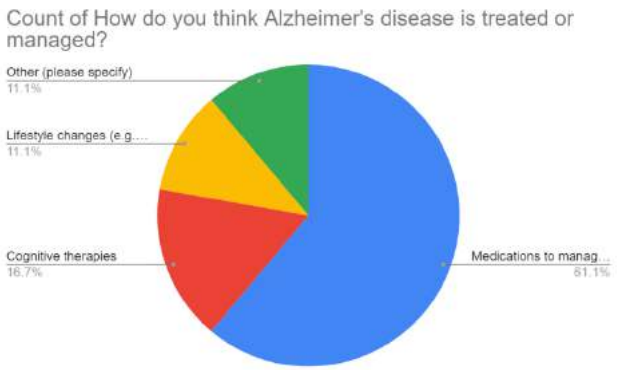

Figure 4.16: Respondents take on treating or managing Alzheimer's disease

Medications are the most common way people believe Alzheimer's disease is managed, at 61.1%. This is followed by lifestyle changes (e.g., diet, exercise) and cognitive therapies, both at 16.7%. Other ways of managing Alzheimer's disease, unspecified in the pie chart, account for 11.1%.

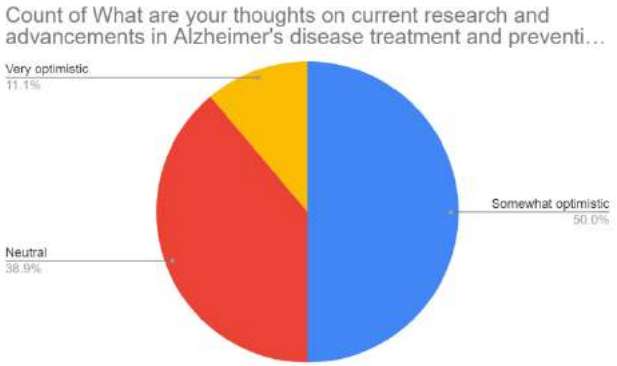

Figure 4.17: Respondents take on current research and advancements in treatment of Alzheimer's disease

Based on the pie chart, there is a neutral sentiment (38.9%) regarding current research and advancements in Alzheimer's disease treatment and prevention. A somewhat optimistic view is held by 50% of respondents, and a very optimistic view is held by 11.1%.

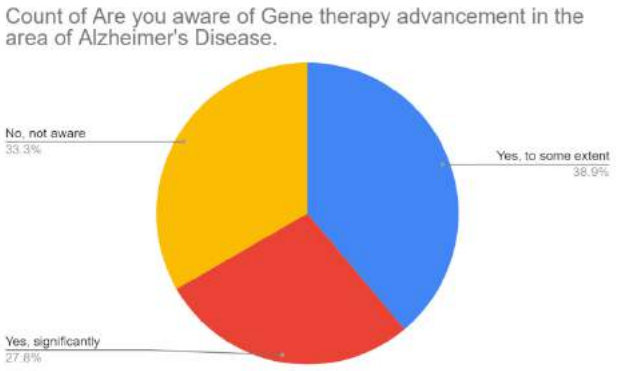

Figure 4.18: Awareness about Gene therapy advancements in the area of Alzheimer's disease

Based on the pie chart, around 33.3% are not aware of gene therapy advancements in Alzheimer’s disease. Only a small portion, 27.8%, are significantly aware and 38.9% are aware to some extent**.**

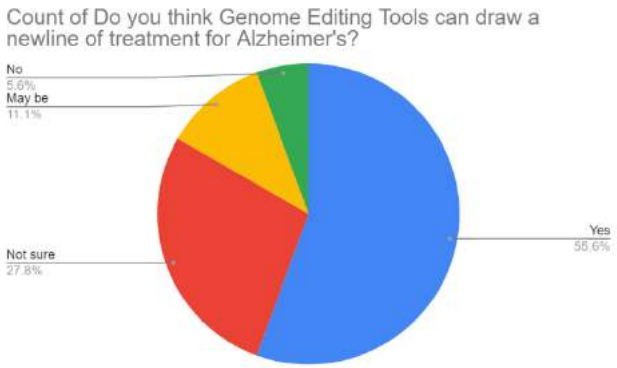

Figure 4.19: Take on Genome editing tool in treatment of Alzheimer's disease

Based on the pie chart, a majority of people believe that genetic editing tools can be a new line of treatment for ALS. 55.6% of respondents said yes, while 27.8% were not sure, 11.1% said maybe, and only 5.6% said no.

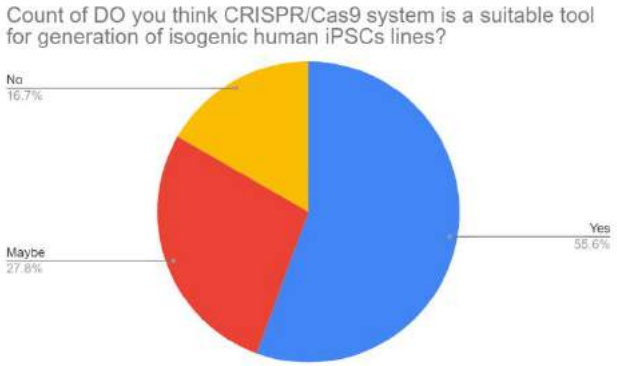

Figure 4.20: Count on CRISPR/Cas9 system is a suitable tool for generation of isogenic human iPSCs lines.

Based on the pie chart, a majority of respondents (55.6%) believe that the CRISPR/Cas9 system is a suitable tool for generating isogenic human iPSC lines. 27.8% of respondents were unsure, and 16.7% said no.

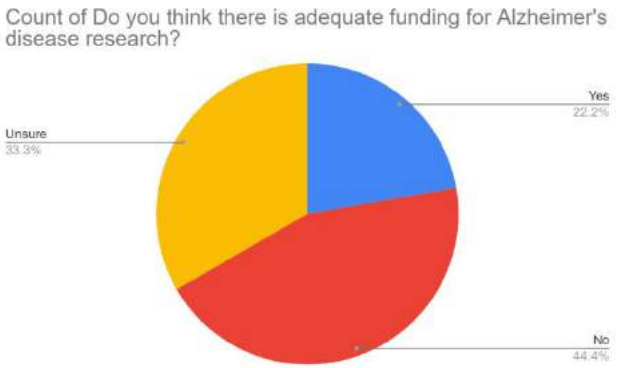

Figure 4.21: Respondents take on adequate funding for Alzheimer's disease

Based on the pie chart, 44.4% of respondents believe there is not adequate funding for Alzheimer's disease research. 33.3% are unsure and 22.2% believe there is adequate funding. This pie chart suggests that a significant portion of the population believes there is not enough funding for Alzheimer's disease research.

Chapter 5 Discussion

The present review study highlights the urgent need for innovative approaches to treat Alzheimer's disease, pointing out the drawbacks of current treatments while also emphasizing the potential of customized medications like CRISPR/Cas9. This encourages a review of the quickly evolving area of Alzheimer's research and therapy as well as an investigation of the ethical concerns surrounding human genome editing, particularly with regard to its potential use in addressing hereditary factors associated with the disease. According to the survey study results conducted with two participant groups (the general group and the research group), while both groups showed a basic understanding of Alzheimer's symptoms and risk factors, the research group's awareness of genetic influences and cutting-edge technologies like CRISPR/Cas9 for potential therapeutic interventions was noticeably higher. Remarkably, the general public was more interested in the pragmatic aspects of the disease, like caregiver support services and the effects on society. This implies that although exposure to academic settings improves understanding of scientific ideas surrounding Alzheimer's disease, there is a need to close the knowledge gap between the general public and the ramifications of the disease for society. These results highlight the significance of all-encompassing education initiatives that combine scientific discoveries with practical applications to promote widespread understanding and support for Alzheimer's disease. It is underlined that progress depends on collaboration between several businesses, including pharmaceutical corporations, clinicians, and researchers. This thought exchange may lead to conversations on how to improve interdisciplinary collaboration, accelerate research, and ensure equitable access to any future developments in Alzheimer's treatment.

Chapter 6 Summary

The review summarizes latest advancement of Alzheimer’s disease, in terms of gene therapy/genomic editing as majority of pathogenesis relying on the facts that basis and advance mutation are governing the pathogenesis of AD. Targeting/modifying/rectifying those entities/genes may pave a way to advance therapeutics of AD. CRISPR/Cas9 gene editing, Alzheimer's disease incidence, therapies, and the consequences of these developments. The present study also highlights the need for new drugs and therapies by emphasizing the serious effects and rising incidence of Alzheimer's disease. Gene therapy offers focused molecular intervention, whereas currently available drugs just address symptoms. Targeting the genetic elements of Alzheimer's disease through precise gene modification is made possible by the CRISPR/Cas9 gene editing technique. In addition, survey data about the general public's knowledge, views, and comprehension of Alzheimer's disease as well as prospective applications of gene therapy and technology in the illness's treatment included in the study gives a perspective to look into the side mirrors. The financial toll that Alzheimer's causes globally is also discussed, emphasizing the necessity for further research and advancements in current therapies.

Chapter 7 Conclusion

In Conclusion, the growing incidence of Alzheimer's disease and its severe effects on both individuals and families make it an ongoing public health concern. Current therapies try to control symptoms and delay the disease's course, but they are unable to provide a permanent cure, which emphasizes the critical need for new discoveries. Targeted medicines appear to be a promising route due to recent advancements in Alzheimer's research, especially in gene editing tools such as CRISPR/Cas9. It may be possible to modify the course of Alzheimer's disease by correcting genetic changes linked to the illness using gene editing. Studies examining the safety and effectiveness of CRISPR/Cas9 technology in treating Alzheimer's disease are currently in progress. Treatment options for Alzheimer's disease are changing even as we wait for conclusive results from continuing research. Realizing discoveries that could improve the prognosis for people with Alzheimer's disease requires close collaboration between researchers, physicians, and pharmaceutical companies.

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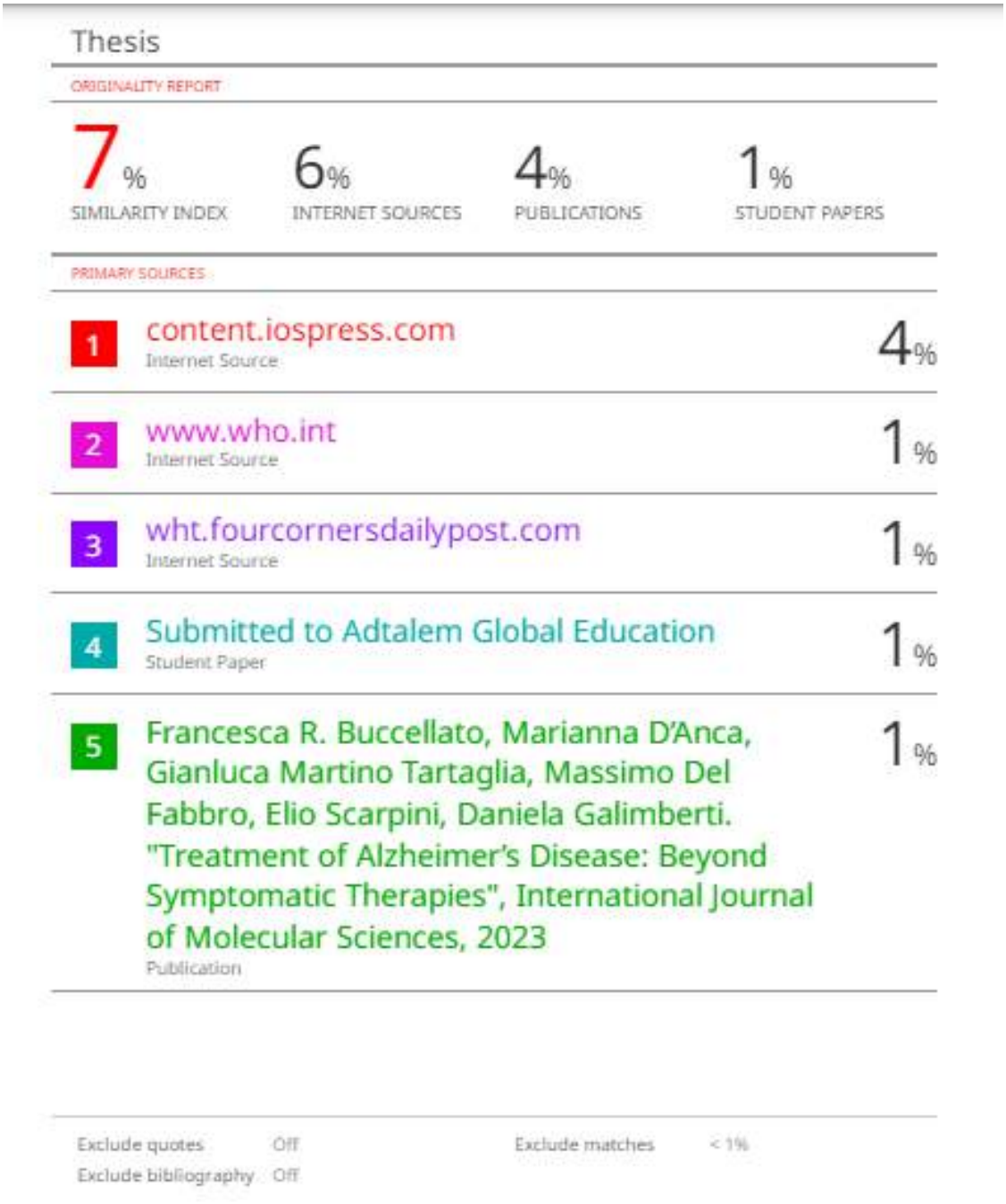

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