



DEVELOPMENT OF TARGETED THERAPIES FOR ALZHEIMER'S DISEASE & LECANEMAB IN TREATMENT OF ALZHEIMER'S DISEASE.

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Abstract: Alzheimer's disease also called as senile dementia. It is a progressive disease that destroys memory & other important mental functions. In this, Brain cells connections & the cells themselves degenerate & die eventually destroying memory & other important mental functions. As the disease advances, symptoms can include problems with language, disorientation, mood swings, self neglect & behavioural issues, etc.. There is a substantial need for new therapies that offer improved symptomatic benefit & disease slowing capabilities. The aged population is growing globally, creating an urgent need for more promising therapies for this debilitating disease. In these there are various drugs are developed for the treatment of Alzheimer's disease e.g.Lecanemab-It is an Amyloid beta targeting antibody used to treat AD. Here we cover the mechanism of action of targeted therapies & therapeutical agents/drugs to rethink drug development strategies & development of targeted therapies for Alzheimer's disease & also directions for further studies.

Key Words – Alzheimer's disease, Amyloid Beta-protein, Tau Protein, Targeted Therapies, Lecanemab, Aducanumab

I.INTRODUCTION : Alzheimer's disease is a progressive & fatal neurological disorder that impairs cognitive & behavioural Functions. It is characterized by the deposition of Amyloid Beta peptides in extracellular plaques & the accumulation of intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein. These protein aggregates disrupt the normal functioning of neurons & trigger a cascade of neuroinflammation, Oxidative stress, synaptic loss & neuronal death. Currently, there is no cure for Alzheimer's disease, & the available treatments provide only symptomatic relief. Therefore, there is an urgent need for the development of targeted therapies that can halt, slow down or prevent the progression of the disease. This paper will review the recent advances in the Understanding of molecular mechanisms of Alzheimer's disease & the development of targeted therapy that aim to mitigate its pathogenesis. In this, Lecanemab is a monoclonal antibody that is being developed as a potential treatment for Alzheimer's disease.

- Brand Name - Leqembi
- Generic Name – Lecanemab.

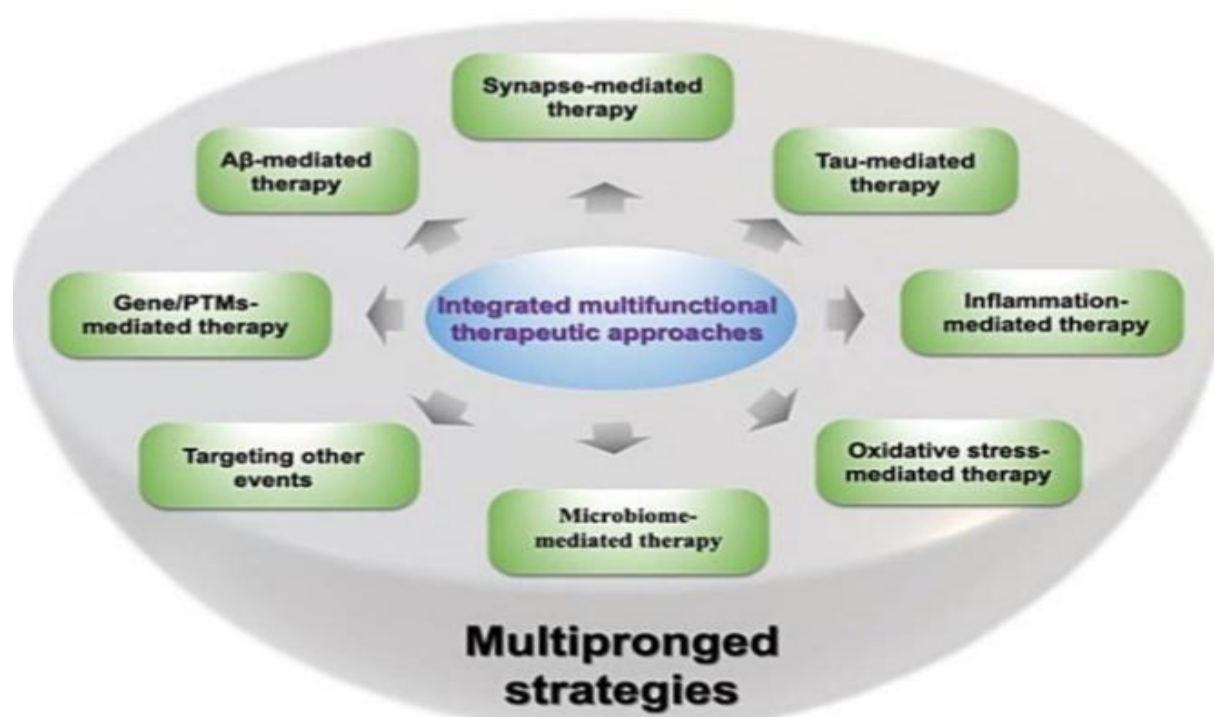
II. PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE : The beta-amyloid deposition & neurofibrillary tangles lead to loss of synapses & neurons, which results in gross atrophy of the affected areas of the brain, typically starting at the mesial temporal lobe. The pathology of Alzheimer's disease is characterized, in part, by extracellular ABeta deposits, commonly referred to as plaques, as well as intracellular tau 3 protein tangles. The inherently disordered, aggregation prone ABeta peptide remains an extremely challenging system to work with.

III. MOLECULAR MECHANISM OF ALZHEIMER'S DISEASE : Alzheimer's Disease is a complex & multifactorial disorders that involves Multiple biological pathways & networks.The accumulation of Amyloid-Beta peptides & tau protein is considered the hall mark of Alzheimer's disease Pathogenesis. However, recent evidence suggests that the formation & propagation of these protein aggregates are influenced by various factors, such as genetics, environment, lifestyle & comorbidities.

IV. TARGETING THERAPIES FOR ALZHEIMER'S DISEASE : Several Therapeutic strategies have been proposed to target different aspects of Alzheimer's disease Pathogenesis. These approaches can be classified into four main categories like :-

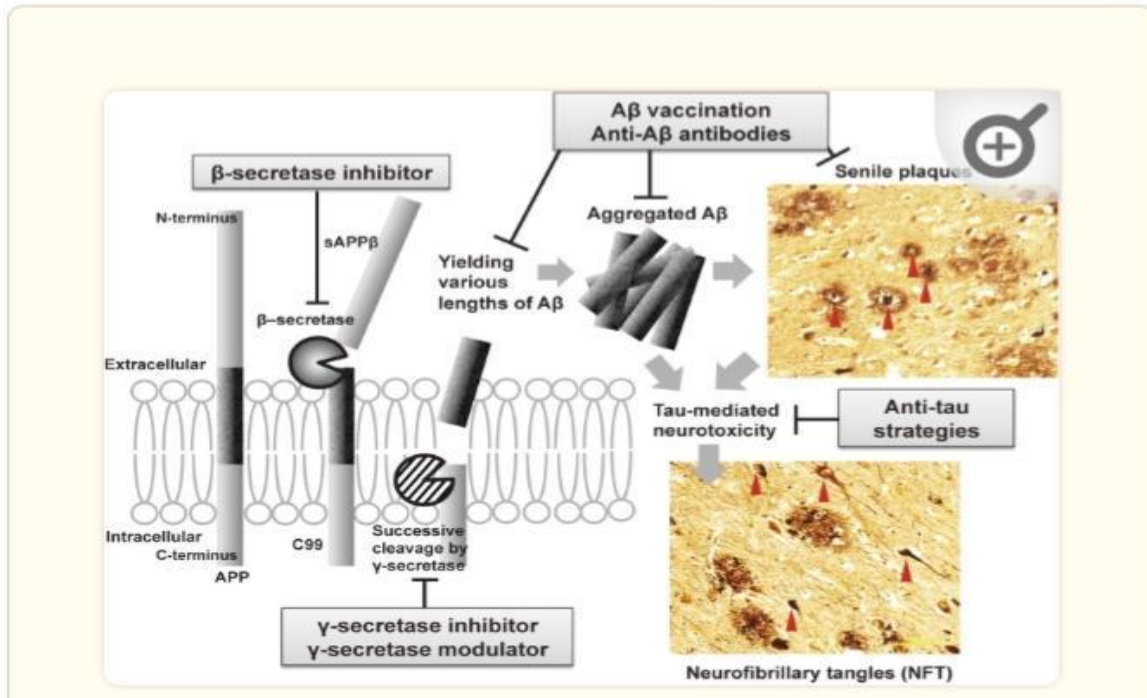
- 1) Anti-amyloid therapies
- 2) Anti-tau therapies
- 3) Anti- Inflammatory Therapies
- 4) Neuroprotective therapies.

Fig. 1.1- Proposed multipronged therapeutic strategies to target multiple toxicities of AD Pathology



- 1) **Anti-amyloid Therapies**:- The anti-amyloid therapies aim to reduce the accumulation of Amyloid Beta peptides & their toxicity. These treatments include immunotherapies, small molecules & gene therapies. Immunotherapies use Monoclonal Antibodies/Vaccines to target amyloid beta peptides & enhance their clearance by the immune system. Small Molecules such as BACE inhibitors, gamma-secretase Inhibitors & aggregation inhibitors interfere with amyloid beta production, processing, or aggregation. Gene therapies involve the delivery of viral Vectors / Nanoparticles carrying genes that encode enzymes / antibodies targeting amyloid-beta.
- 2) **Anti-Tau Therapies** :- The anti-tau therapies aim to reduce the accumulation of Tau protein & its hyperphosphorylation. These treatments include small molecules & Immuno therapies. Small Molecules such as kinase inhibitors, microtubule stabilizers & heat shock proteins modulate the activity/stability of Tau protein. Immunotherapies use Monoclonal antibodies / vaccine to target tau protein & enhance its clearance by the immune system.
- 3) **Anti –Inflammatory Therapies** :- These anti-inflammatory therapies aim to reduce the neuroinflammation & oxidative stress associated with Alzheimer's disease. These treatments include; non-steroidal antiinflammatory drugs (NSAIDs), cytokine inhibitors, & antioxidant agents NSAIDs such as aspirin, ibuprofen. & naproxen reduce the production / activity of pro-inflammatory mediators. Cytokine Inhibitors such as TNF- α blockers & LLIF blockers modulate the signalling pathways involved in neuroinflammation. Antioxidant agents such as Vit C & E COQ 10 resveratrol scavenge the reactive oxygen-species that damage neurons.
- 4) **Neuroprotective Therapies** :- The neuroprotective therapies aim to enhance the survival & function of neurons & their synapses. These treatments include growth factors, neurotrophins. & metabolic enhancers. Growth factors such as GDNF, BDNF & IGF-1 promote the survival & growth of neurons & their dendrites. Neurotrophins such as NGF, NT-3 & NT-4/5 enhance the synaptic plasticity & memory formation. Metabolic enhancers such as ketone bodies, glucose analogs. & mitochondrial biogenesis modulators enhance the energy, metabolism & resilience of neurons.

5) **Cholinergic drug therapy** :- The neuropathology of AD is characterized by an early loss of basal forebrain cholinergic neurons, leading to a deficiency in cholinergic neurotransmission. The deficiency plays an imp. Role in learning into the synaptic cleft & binds to muscarinic nicotinic



receptors present on post synapse.

Fig. 1.2 –Therapeutic strategies for Alzheimer’s disease based on the amyloid hypothesis. Aβ is produced by a two-step sequential cleavage of APP by B-secretase and γ-secretase. Toxic Aβ fragments aggregate and finally form plaques. Tau-mediated neurotoxicity and NFT formation are considered to be downstream events in the amyloid cascade. Most DMTs currently under development target steps in the amyloid cascade.

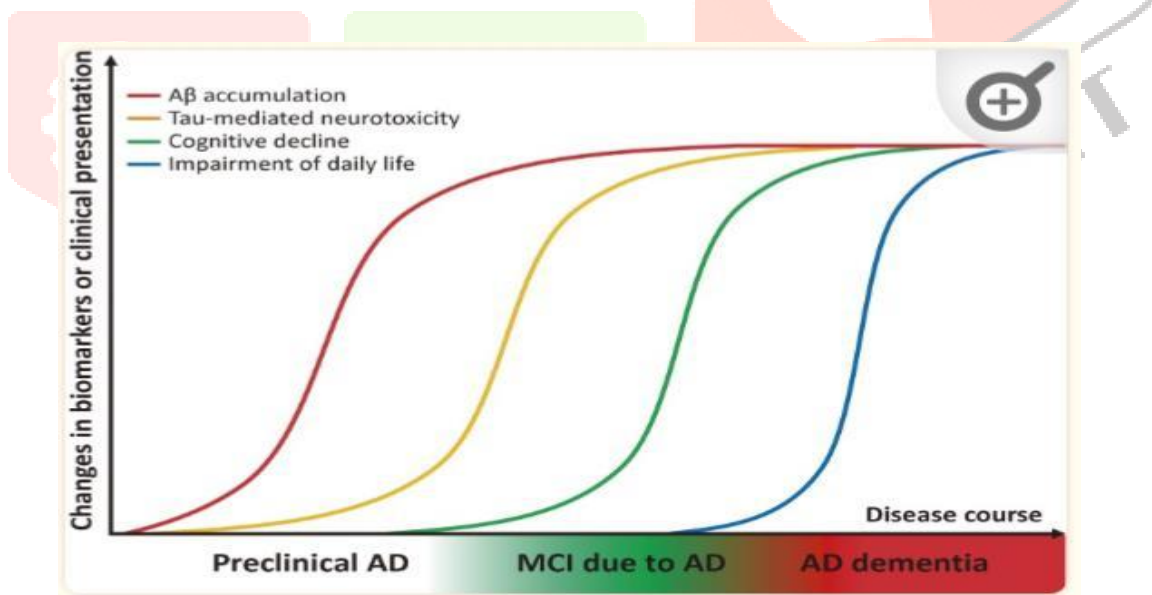


Fig. 1.3 –Hypothetical model of biomarker changes and proposed new clinical staging of AD. Accumulation of Aβ and subsequent manifestation of tau-mediated neurotoxicity begin roughly 10-20 years prior to the onset of dementia MCI due to AD is a prodromal phase of AD, i.e., an intermediate phase between normal cognitive functioning and dementia. Preclinical AD is a stage earlier than MCI in which cognitive function is normal but the presence of amyloid pathology is suggested by biomarkers.

V. DRUG – LECANEMAB USE IN TREATMENT OF ALZHEIMER'S DISEASE:-

The Food & Drug Administration (FDA) recent granted accelerated approval to a new Alzheimer's treatment called Lecanemab which has shown to moderately slow cognitive Functional decline in early-stage cases of the disease. Lecanemab is an amyloid beta- targeting antibody used to treat Alzheimer's Disease in patients with Mild cognitive impairment / Mild dementia with a known amyloid beta pathology

Summary : Brand Name – Leqembi

Generic Name – Lecanemab

Lecanemab is a recombinant humanized immuno globulin gamma I (Ig t1) monoclonal antibody directed against aggregated soluble & insoluble forms of amyloid beta (AB), which are implicated in the pathophysiology of Alzheimer's disease. Lecanemab works to reduce ABeta plaques & prevent A beta deposition in the brain, with high selectivity to Abeta proto fibrils. On January 6, 2023, Lecanemab was accelerated approval by the FDA for the treatment of Alzheimer's Disease. In clinical trials, it significantly reduced brain ABeta plaques compared to placebo

- 1) **Pharmacodynamics-** Lecanemab reduces amyloid- beta(ABeta) plaques in dose & time dependent manner in clinical trials
- 2) **Mechanism of action -** Amyloid - B (Abeta) Plaques are a hallmark pathology of Alzheimer's disease (AD); making them a desirable therapeutic target for Potential drugs for treating AD The production & accumulation of AB plaques in the brain are commonly observed in AD & distinct characteristics of AB plaques such as the Solubility, quantity, & composition of AB pools may affect the disease state. AB causes Synaptic impairment neuronal death, & progressive neurodegeneration, which leads to dementia & cognitive impairment associated with AD. AB peptides exist in various conformational states including soluble Monomers, soluble aggregates. of increasing size, & insoluble fibrils & plaque. Soluble Abeta aggregates such as A beta protofibrils are more neurotoxic than Monomers or insoluble fibrils. Lecanemab is an antibody that lowers Abeta plaque in the brain. It preferentially targets soluble aggregated Abeta & works on Abeta oligomers, protofibrils & insoluble fibrils.
- 3) **Metabolism -** Lecanemab degraded by proteolytic enzymes in the same manner as endogenous IgGs.

Half life: The terminal Half-life Ps 5 to 7 days Lecanemab works by removing a sticky protein from the brain that is believed to cause Alzheimer's disease to advance. It is very exciting because this is the 1st treatment in out history that shown an unequivocal slown Of decline in Alzheimer's disease, says Dr. van Dyck.

Why is Lecanemab better than Aducanumab?

- In clinical trials Lecanemab has been shown to remove amyloid more quickly than Aducanumab other medication called gantenerumab.
- Lecanemab has also shown a lower incidence of a side effect called ARIA (amyloid-related imaging abnormalities) compared to Aducanumab in Clinical trials.

How does lecanemab work?

-Lecanemab is a disease modifying immunotherapy drug. It works with the body's immune system to clear amyloid protein build up from the brains of people living with early- stage Alzheimer's disease.

-These amyloid protein build ups are thought to be toxic to brain cells, causing them to get sick and eventually die, leading to the symptoms of Alzheimer's disease. Immunotherapies are already used in medicine, for example in the treatment of some cancers. More specifically, lecanemab is an antibody treatment. Antibodies already exist in the human body - they are a type of protein produced by the body's immune system to fight against disease.

-Lecanemab is given to patients intravenously, which means into a vein through a drip bag. It targets amyloid protein in the brain and then 'triggers' the brain's immune system to clear it out.

- 4) **Clinical Trials -** Late last year, Eisai (the company that makes lecanemab) released the full results of lecanemab's phase 3 clinical trial called Clarity- AD at the Clinical Trials on Alzheimer's Disease (CTAD) conference in San Francisco on the 29th November 2022. Clarity-AD is a phase 3 clinical trial involving 1,795 people. The trial involved people living with early-stage Alzheimer's disease who have amyloid protein build ups in their brains. Half the participants were given lecanemab and half received a dummy drug over 18 months.. The trial showed that lecanemab slowed down the speed at which memory and thinking skills got worse by 27% in people taking the drug compared to people on the dummy drug. Researchers estimate over 18 months the drug may slow the progression of the condition by about 7 months. The research team also found that the drug slowed the decline in quality of life by up to 56%. Importantly, the drug reduced the amount of amyloid protein present in the brain. Amyloid protein levels were also reduced in the blood and spinal fluid. Clinical trials for lecanemab will continue so that researchers can understand the effects of taking this drug over a longer period of time.

Who could benefit from lecanemab treatment?

Lecanemab is a treatment for people with early-stage Alzheimer's disease who have amyloid in their brain This means people with other types of dementia, or in the later stages of Alzheimer's disease, are unlikely to benefit from this drug.

Does lecanemab have any side effects?

Like all drugs, lecanemab was found to have some side effects. During the clinical trial, some people taking lecanemab experienced reactions to having the drug infused, while some others were found to have swelling or microbleeds in the brain in response to lecanemab - known as Amyloid Related Imaging Abnormalities or ARIA. The majority of people who experienced ARIA had no symptoms and these changes in the brain were only detected using MRI brain scanning.

Lecanemab (BAN2401) is a monoclonal antibody that is being developed as a potential treatment for Alzheimer's disease.

1. Lecanemab has shown promising results in reducing the progression of Alzheimer's disease. In clinical trials, it has demonstrated the ability to reduce amyloid beta plaques in the brain that are characteristic of Alzheimer's. Furthermore, it has also been shown to slow down cognitive decline in some patients.

2. LECANEMAB TARGETS A SPECIFIC FORM OF AMYLOID BETA, KNOWN AS PROTOFIBRILS, WHICH ARE THOUGHT TO BE ESPECIALLY TOXIC TO BRAIN CELLS. OTHER ANTIBODIES THAT TARGET AMYLOID BETA HAVE NOT BEEN AS EFFECTIVE AT REDUCING COGNITIVE DECLINE. LECANEMAB'S ABILITY TO TARGET TH

is specific form of amyloid beta is a unique feature that sets it apart from other potential treatments for Alzheimer's disease.

3. Research suggests that lecanemab may be effective at early stages of Alzheimer's disease. In clinical trials, patients with mild cognitive impairment or early Alzheimer's disease who received lecanemab showed a reduction in cognitive decline compared to those who received a placebo. The earlier the treatment, the better chances of slowing down the progression of AD.

4. Lecanemab has also shown potential in combination therapy with other drugs. Researchers are testing a combination of lecanemab and a BACE inhibitor, which targets the production of amyloid beta, to determine if it can deliver a more significant benefit than either drug alone.

5. Lecanemab is currently in Phase III clinical trials, which will provide additional insight into its effectiveness as a treatment for Alzheimer's disease. The results from these trials will be key in determining if lecanemab becomes an approved therapy for Alzheimer's disease.

VI. Development of therapies for alzheimer's diseases :-

1. Targeting inflammation may be a promising approach in Alzheimer's drug development. Recent studies suggest that inflammation plays a critical role in the progression of Alzheimer's. Modulating immune responses could, therefore, be an effective way to slow down the progression. Various clinical trials are currently ongoing or planned to test drugs targeting inflammation pathways.

2. Precision medicine approaches are gaining momentum in Alzheimer's drug development. Researchers are using genetic and biomarker information to identify different subtypes of Alzheimer's disease. Based on these subtypes, they aim to target specific molecular pathways underlying the disease. A better understanding of the molecular basis of the disease could allow for more targeted and effective drug development.

3. Neurotrophic factors are promising candidates for Alzheimer's therapies. Neurotrophic factors are molecules that help support the survival and function of neurons. Recent research has shown that decreasing levels of neurotrophic factors may be a contributing factor to Alzheimer's. Increasing these levels through drug therapy could help protect neurons and slow the progression of the disease.

4. Targeting tau protein accumulation is a promising approach in Alzheimer's drug development. Tau proteins play an essential role in stabilizing the structure of neurons. In Alzheimer's, tau proteins accumulate abnormally and form tangles, leading to neuronal damage. Recent research suggests that targeting the excessive accumulation of tau proteins could help slow or prevent the progression of Alzheimer's. Several drugs targeting tau proteins are in various stages of clinical development.

VII. CURRENT RESEARCH UPDATES ON AD THERAPEUTICS :

1) Improvement and Innovation of Current Medicine -

There is a direction of research on recombination therapy and pharmacological improvement of current drugs. Some first-generation drugs like cholinesterase inhibitors (donepezil etc.) have been used for several years while it was found that side effects may develop after administration of high dosages of these drugs. However, new research demonstrated that a fixed-dose combination (FDC) could contribute to drug efficacy. Current clinical trials indicated that combined therapy with donepezil and extended-release memantine is not only effective in treating patients with moderate to severe Alzheimer's disease, but also reduces the side effects caused by donepezil.

2) Progress of Stem Cell Replacement Therapy for Alzheimer Disease -

Patients at the moderate to late stage of AD usually suffer from serious memory loss and disability due to neuronal cell clearance in the brain. Cell regeneration by reactivation of stem cells from the patients could be the right way for minimizing neuronal recovery. Hence, stem cell replacement therapy (STRT) could be one of the solutions for neuronal cell regeneration. Cell replacement therapy for AD usually can be categorized into use of (i) mesenchymal stem cells (MSC) for total replacement of healthy primary stem cells for neuron regeneration and suppression of pathological factors, (ii) neural stem cells (NSC) for direct development of astrocytes, (iii) genetically modified cells (GMC) for gene edited stem cell transplantation with silent AD activators and (iv) induced pluripotent stem cells (iPSC) with most functions of MSC and availability for using the cells from patient themselves.

Since 2016, there have been ongoing or planned clinical trials of stem cell replacement therapy for AD in China, Korea and USA which have been registered in US National Institute of Health. A Korean team undertook 4-year STRT project (Project ID: NCT2054208) for a randomized, double-blinded, phase 1/phase 2 clinical trial involving intraventricular

injection of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSC). A Chinese team undertook a 35-year STRT project (NCT02672306) involving a randomized, double-blinded, phase I/phase 2 clinical trial by employing intravenous injection of HUCH-MSC. A US team is going to conduct a STRT project (NCT02600130) with a duration of 2 years and 10 months for a randomized, placebo controlled, double-blinded phase I clinical trial based on intravenous injection of human MSC. It is difficult for MSC-based clinical trials to obtain an approval because of concerns about ethical issues. Hence, some researchers have started to move on to iPSC-based neuronal recovery. Romanyuk et al conducted an experiment on rat spinal cord repair by iPSC-derived neural precursor (iPSC-NP) transplantation. The results showed that iPSC-NP could trigger various neural growth factors & brought about the recovery of both white matter & grey matter in the spinal cord.

3) Immunotherapy for Alzheimer's Disease -

As mentioned above, there are two pathological hallmarks, of AD ie. All peptide aggregation and tau phosphorylation. Immunotherapy of AD usually focuses on A β attenuation because AB aggregates work as an initiator of AD pathogenesis and cause major disruption in the brain. In fact, studies on anti-A monoclonal antibodies (mAbs) have started decades ago while the efficacy and delivery of some candidate mAbs varied and some drug developers continue to carry out structural modification of therapeutic mAbs. Current clinical trials of mAbs could be categorized into trials employing sequence-specific mAbs and those using conformation-specific mAbs.

Liu et al. reviewed the current clinical studies on immunotherapy in Alzheimer's disease.

In the recent 10 years, immunotherapy against Alzheimer's disease mainly focused on attenuation of pathological A β and tau and vaccination of A β and tau to activate the innate immune response.

Xing et al. found that a monoclonal antibody 3F5 against A β e, by targeting N-terminal 1-11 amino acids, could prevent AB aggregation and the corresponding neurotoxicity. 3F5 might trigger the depolymerization of AB fibrils and endocytosis by microglia that attenuated the death of neurons. It might reduce the rate of cognitive deficit.

An SH-SY5Y cell-based research also illustrated that administration of monoclonal antibody against A β e N-terminal 1-16 amino acids could effectively inhibit endosome EEA1 and lysosome, and rescue the cell surface expression of high-affinity choline transporter (CHT), CHT was paramount in choline uptake and ACh generation in neurons.

VIII. FUTURE DEVELOPMENTS :

i) Transcriptional Approaches to Drug Repositioning in AD :-

To identify novel compounds for repurposing or repositioning, additional strategies are needed. One such approach is transcriptional profiling. A disease or injury will alter gene expression in a characteristic manner in a cell or tissue, which will produce a "transcriptional signature." A transcriptional hypothesis proposes that a drug altering the transcriptome in an opposing manner to the disease may have a therapeutic benefit by counteracting potential pathological pathways. The Connectivity Map (CMAP) collaboration produced transcriptional signatures for 1,300 drugs or natural compound profiled on three cancer cell lines 1411. CMAP has been complemented by the Library of Integrated Network-based Cellular Signatures (LINCS) program, which examined changes in 1,000 "landmark" transcripts for an additional 20,000 compounds, using algorithms to impute changes in expression of transcripts that were not quantified directly.

Transcriptional profiles are widely published and available through meta-analysis platforms such as SPIED for early, mid, and late stages of AD and other dementias, and for preclinical mouse models. Using this approach in CMAP, 153 drugs were identified with signatures that significantly inversely correlate with the AD transcription signature, the majority of which retained this profile in further studies using human induced pluripotent stem cell-derived cortical neurons. Based on these studies, the top 78 candidate drugs were taken forward to an in vitro screening program with six independent assays the impact on different aspects of AD pathology. Nineteen (24%) of the agents were hits in at least two assays, with 15 being novel or emerging candidates known or likely to be brain penetrant (some examples are shown in Table 5.1). Importantly, in addition to identifying novel candidates for further evaluation, this supports the hypothesis that transcriptional profiling may be a useful way of identifying or triaging compounds for in vitro screening. Other hits included drugs already highlighted as potential repositioning candidates in AD, including metformin, nabumetone, and several flavonoids.

The global transcriptional signatures identified above were generated without considering the functions of the individual transcripts or the established mechanism of drug action. In other words, this is a "black-box" approach that operates independently of any mechanism-based hypothesis. Almost 30 risk genes have now been identified for AD and the identification of drugs that alter the expression of some of these, or another endogenous gene with known therapeutic potential, provides for a hypothesis-driven approach to drug repositioning. There are no well-developed cases for this in AD yet, but there are promising emerging candidates for other neurodegenerative diseases using this approach

ii) Targeting Risk Genes and Growth Factors :-

Rather than increasing the expression of a protective gene, other studies have sought to identify candidate drugs that reduce the expression of a risk gene. Although this approach has not yet been widely used for AD, there is an interesting recent example of this strategy for Parkinson's disease (PD) where reducing betasynuclein transcription may have therapeutic benefits [48]. A screen of the Food and Drug Administration (FDA) library demonstrated that alpha-2-adrenergic agonists such as salbutamol

suppress this transcription, and subsequent work has also suggested that salbutamol offers some protection in a preclinical model of PD [49]. Future clinical trials will be needed to verify this approach, but nonetheless similar approaches targeting risk genes in AD may offer a use strategy of identifying further candidate therapies.

IX. CONCLUSION :-

Alzheimer's disease is a devastating neurological disorder that poses a major challenge to public health. The development of targeted therapies that can modulate the molecular mechanisms of Alzheimer's disease holds great promise to improve the lives of affected individuals and their families. The anti-amyloid, anti-tau, anti-inflammatory, and neuroprotective therapies reviewed in this paper represent a diverse and evolving landscape of approaches that can be combined or customized according to the individual characteristics of patients. Moreover, the identification of biomarkers and the use of advanced technologies such as proteomics, genomics, and imaging can facilitate the early detection, diagnosis, and monitoring of Alzheimer's disease and the evaluation of the effectiveness of targeted therapies.

Lecanemab treatment resulted in significant reduction in amyloid plaques and a slowing of clinical decline. Data indicate that rapid and pronounced amyloid reduction correlates with clinical benefit and potential disease-modifying effects, as well as the potential to use plasma biomarkers to monitor for Lecanemab treatment effects.

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