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Advances in Therapeutic Strategies for Alzheimer's Disease: Bridging Basic Research and Clinical Applications

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Abstract : This book summarizes new developments in therapeutic strategies for Alzheimer's disease (AD) and how to translate basic research to the clinic. AD is a heterogeneous and difficult disease to diagnose. No current treatment can modify the development and progress of the disease or delay the appearance of neurodegeneration. The failure of multiple drug candidates is attributed to a lack of understanding of AD pathophysiology, including the factors that promote neurodegeneration, the variances in patient populations that may reflect distinct but overlapping disease mechanisms, and the limited ability to predict the efficacy and safety of drug treatments. The articles compiled in this book attempt to describe what we consider the most important problems and challenges to advancing therapeutic strategies. The objectives of this book are to bridge the gap between basic and clinical research, questioning current concepts or finding new ideas to identify susceptible patients, slow down AD, and develop new drugs or new approaches for AD therapy. All the chapters in this book have scientific originality or present different views on exciting aspects of AD treatment.

There are several classes of drugs with a confirmed or potential beneficial effect on AD symptoms, but there is not a single therapeutic agent that can slow or arrest neurodegeneration. Though the scenario is bleak, the emergence of new avenues such as antibodies against tau pathology, tau-tubulin interaction inhibitors, or hippocampal stimulation by optogenetics show potential for the development of new AD treatments. Potential AD therapies targeting gut microbiota, astrocytes, or unique pathways such as those regulating circadian rhythms, currently considered to be peripheral components of AD, offer exciting therapeutic strategies, opening the door to the slow or arrest neurodegeneration processes that define AD.

Keywords: Alzheimer's Disease Therapy, Translational Research for AD, Neurodegeneration Mechanisms, Heterogeneous AD Pathophysiology, AD Drug Development Challenges, Predictive Efficacy in AD Treatments, Tau Pathology Antibodies, Tau-Tubulin Interaction Inhibitors, Hippocampal Optogenetic Stimulation, Gut Microbiota in AD Therapy, Astrocyte-Targeted Treatments, Circadian Rhythm Pathway Modulation, Neurodegeneration Arrest Strategies, Patient Stratification in AD, Clinical and Basic Research Bridge, Innovative AD Therapeutic Approaches, Failures in AD Clinical Trials, AD Susceptibility Identification, Peripheral Pathways in AD, Future Directions for AD Treatment.

1. Introduction

Ever since the diagnostic criteria of Alzheimer's disease (AD) were established in the mid-1970s, there has been hope that effective immunologic approaches could be used to ameliorate the disease or prevent its progression. Research into the mechanisms causing the deposition of amyloid in senile plaques and tau tangles in neurofibrillary degeneration in AD has generated a steady stream of therapeutic possibilities. However, clinical translation has been dishearteningly slow. Commencing in the 1990s, trials of immunologic intervention in persons with established AD have shown only modest, if any, effects on clinical measures of illness. Even so, antibody pharmacotherapy directed at amyloid was approved recently in some countries for use in AD patients. Efforts to develop other immune interventions for early symptomatic treatment are ongoing.

Recent studies of patients with rare familial AD mutations, and more recently of patients with early-emergent sporadic AD, have suggested that by the time clinical manifestations of AD appear, it may be too late for an amyloid-targeted immunotherapy to be effective. More pointedly, it is unclear whether the currently approved antibody therapies for AD patients can have any effect, given their extreme delay in treatment. Nonetheless, a patient-centric need for such therapies remains, as symptomatic treatments for AD remain inadequate and no other disease-modifying therapies are currently in use. Ultimately, new concepts and options are warranted. Given that an AD diagnosis implies the presence of these potentially toxic proteins in the brain, other immunotherapeutics that work directly through clearance rather than through inhibition of function may thus yield better results. These concepts plus exciting new data continue to encourage enthusiasm for potential antibody-based approaches for the treatment of AD.

1.1. Overview of the Study and Its Importance

Recent years have seen an increase in the number of promising polypeptide- and small-molecule therapeutics for Alzheimer's Disease (AD), as well as promising therapeutic strategies including novel biomarker designs and novel drug-focused Gene Therapy. However, the translational period between basic research and clinical application has rarely been bridged for these therapeutics and therapeutic strategies yet. The present text starts by overviewing the clinical presentation of AD and its pathological hallmarks and risk factors, before introducing more specific candidates for AD-targeting and therapeutic strategies. The latter include Aβ-targeting and Tau-targeting and synaptogenic therapy strategies and approaches for treating both sporadic AD and familial AD variants, aside from tau protein kinase cGMP-inhibited protein kinases being novel AD risk factors for sporadic AD. Other approaches include utilizing novel protein structures identified from technology to identify related candidate proteins for molecules exhibiting diagnoses-based adaptive distributing functions in AD postmortem brains and other brain disorders. Here, two major – yet strikingly novel – directions include both metal-element-salted peptide receptor/ion channels and peptide synaptogenic drugs being employed for combating AD. In addition, we will also propose biomarker designs to guide translational with a new strategy towards AD drug development, including sensitive and novel strategies for biomarker-guided peptide-based drug design for AD. Making use of expanded pTRs, we will also propose both baseline assessments and kinetics for using and targeting soluble oligomerized structures in AD for all possible present-day AD-targeting therapeutic strategies.

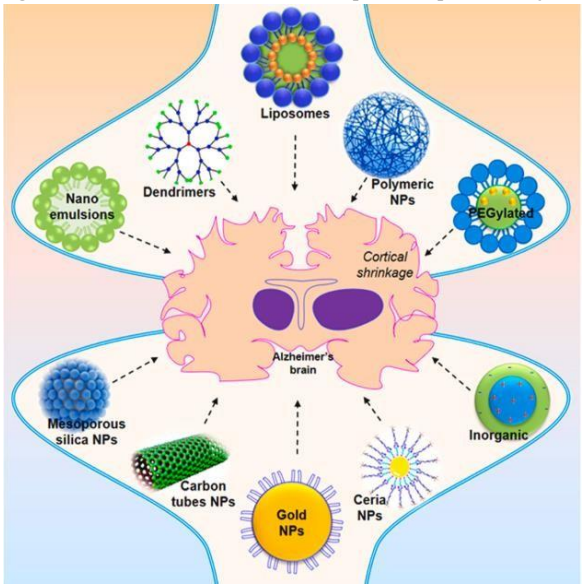

Fig 1 : Advances in developing therapeutic strategies for Alzheimer's disease

2. Understanding Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder in the Western world. It is a multifactorial disease that cannot be simply understood as a consequence of a distinct neurobiological change. Many variables are implicated during the life of individuals who will later develop AD. The emergence of weak detection methods and the absence of curative and preventive strategies have led the focus to the more fundamental aspects of AD pathophysiology, being the triggering factor of the subsequent research dedicated to the development of effective treatments. In this section, we will review the currently available information regarding AD pathophysiology, including the implication of genetic and environmental factors.

Alzheimer's disease is the leading cause of dementia. Although it was first clinically described at the end of the 19th century, it became popular after the post-mortem observation of neuritic plaque and neurofibrillary tangles. These lesions became the core of the so-called amyloid and tau hypotheses. Mutations in genes encoding amyloid precursor protein and presenilins have shown that the accumulation of beta-amyloid peptide is necessary for the development of AD. However, in most patients, the disease occurs as a sporadic disorder without any family history. In the early nineties, the first report of the association of the Apolipoprotein E4 allele with AD was published, demonstrating that genetic risk factors also can explain some sporadic patients. Very recently, the advent of genome-wide association studies has also reported other genetic risk factors. However, they remain scarce in comparison with the number of genetic variants associated with other neurodegenerative disorders.

Equation 1 : Disease Progression Modeling:

$$D_t = f(A\beta, \tau, N_i, G_f)$$

where:

- D_t = Disease severity at time t
- f = Predictive disease progression function
- $A\beta$ = Amyloid-beta plaque concentration
- τ = Tau protein tangle density
- N_i = Neuroinflammation markers
- G_f = Genetic factors (e.g., APOE-ε4 presence)

2.1. Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive loss of memory and cognitive functions accompanied by neuropsychiatric and behavioral symptoms. Memory impairment coexistence with other cognitive domains compromises the early stages of typical AD. The dementia syndrome is characterized by abnormal intracellular aggregation of hyperphosphorylated tau protein (neurofibrillary tangles), and the accumulation of senile plaques (the extracellular deposition of amyloid-beta peptide) into specific brain areas, adjacent to glial inflammatory processes, oxidative stress, and impaired neurovascular homeostasis. Other pathological features are aggregation of a- and b-synuclein, selective neuronal damage in the locus coeruleus (norepinephrine depletion), sub-cholinergic atrophy (deficiency of the cholinergic neurotransmitter system), and brain insulin resistance.

Clinically, the most prevalent form of AD is sporadic AD with the typical late-onset (after 65 years). It is also the most common type of dementia in elderly people. It can present as an atypical form of cognitive impairment known as posterior cortical atrophy with visual disturbances and a language variant associated with logopenic aphasia and cortical atrophy of the language network. Early-onset familial AD is a form of AD with a pattern of autosomal dominance inheritance, but it is rare in the population, and it is characterized by amyloid and tau pathology, including mutations in the APP gene, presenilin 1, or presenilin 2 genes. Although the pathogenesis underlying typical sporadic AD is not completely understood, the deregulation of amyloid precursor protein processing accelerates Aβ production, and the deposition of senile amyloid plaques eventually triggers tau pathology-induced neurodegeneration and neuroinflammatory changes.

2.2. Genetic and Environmental Risk Factors

Alzheimer's disease (AD) is a multifactorial disorder in which both genetic and environmental factors play a role in the risk of occurrence. Genetic factors are divided into risk factors, or susceptibility genes, that increase the risk of developing the disease, and deterministic genes that always cause the disease. Genetic polymorphisms are very common, affecting every human in some way, therefore a strict definition of genetic risk factor should restrict itself only to those factors whose polymorphic variant has a very high prevalence in case reports. In addition to the genetic factors, environmental factors also play an important role in the risk of AD as shown by the known differences in occurrence among several populations. The interactions between risk genes with each other, and with environmental factors must be fully explored, as it is expected that some common polymorphic variants act in concert with environmental factors to fix the risk or that these variants amplify the adverse influence of environmental factors.

The only deterministic genes identified so far are the genes associated with early-onset familial AD; APP, PSEN1, and PSEN2. However, early-onset familial AD is very rare, with an incidence of less than 1% of all cases. In the past three decades, many risk genes have been reported as susceptible factors for late-onset sporadic AD (LOAD), including the well-studied ε4 allele of Apolipoprotein E, triggering receptor expressed on myeloid cells 2, clusterin, complement factor H, and genes involved in inflammatory processes, lipid metabolism, and brain immunity. Despite considerable evidence for their association with AD occurrence, these genes exhibit a relatively low effect size. Nevertheless, the consortium for the GWAS and other similar efforts worldwide have identified dozens of common risk genes, with the majority of them linked to synaptic function, tau phosphorylation and aggregation, microglial activation, and neuronal injury.

3. Current Therapeutic Approaches

Currently, available treatments for Alzheimer's disease (AD) provide only symptomatic relief and are unable to alter the long-term course of the disease. Cognitive symptoms in AD are often accompanied by neuropsychiatric symptoms, which can severely reduce patient quality of life and increase caregiver burden. Cholinesterase inhibitors (ChEIs) are used for both symptomatic treatment of cognitive decline and also to alleviate neuropsychiatric symptoms. These agents are commonly given to mild and moderate AD patients but have less of an effect when the disease progresses to the moderate to severe stages. NMDA receptor antagonists are a second group of pharmacological agents shown to have effects on cognitive symptoms.

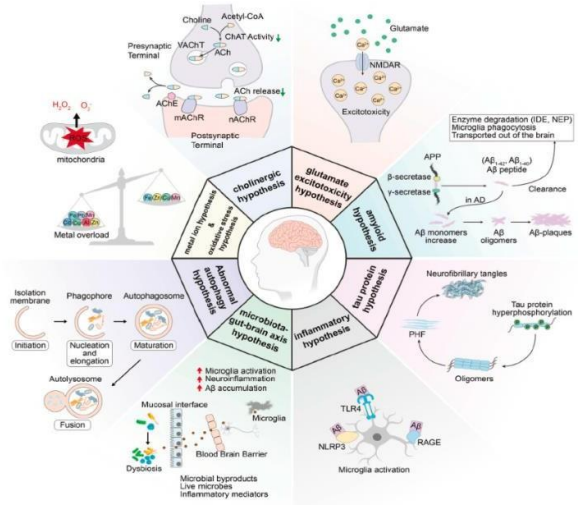

Fig 2 : Therapeutics for the Treatment of Alzheimer's Disease

Cholinesterase Inhibitors

Cholinergic dysfunction has been recognized for decades as one of the major pathways related to the pathological progression of AD. The role of basal forebrain cholinergic neurons is to release acetylcholine (ACh) in the neocortex and hippocampus, the brain regions associated with memory and learning processes. The original stages of AD and the highly abnormal regions are the cholinergic process. Current treatments used for dementia, donepezil, galantamine, and rivastigmine, primarily inhibit the hydrolytic activity of BChE and/or AChE. Donepezil and rivastigmine are used for the treatment of mild to moderate AD.

Glutamate Modulators

The glutamatergic system is the main excitatory neurotransmitter in the healthy brain and plays an important role in learning and memory processes. However, when glutamate levels are abnormally elevated, excessive stimulation of NMDA receptors can produce excitotoxicity, initiating apoptosis and resulting in neuronal degeneration. Because NMDA receptor stimulation and excitotoxicity are considered to accelerate the progression of cognitive impairment, NMDA receptor modulators have been developed. The approved agent on the market is Memantine. It is primarily used for patients with moderate to severe AD when ChEIs are no longer effective.

3.1. Cholinesterase Inhibitors

Given the limitations of currently available therapeutic options for AD, a better understanding of the relation between preclinical and clinical findings could also guide the development of new experimental strategies for the impaired cholinergic system that have a higher chance of success. Patients converge with the underlying neuroanatomical circuit abnormalities described in animal models, and existing drugs can mimic the mechanistic features of these models. It is thus tempting to consider that a combination of existing cholinergic therapies with a discovery-driven approach addressing basic mechanistic flaws in the systems initially described can provide AD patients with communication-enhanced functionality in their daily lives. The cholinergic hypothesis was considered the frontrunner for several years as it relied on the correlation between the depletion of ACh at synaptic sites and cognitive dysfunction and the evidence of the local AD-associated neuroanatomical circuit. There are three sources of ACh signaling, the basal forebrain, the brainstem, and the spinal cord. The forebrain is the main source for projection to the cerebral cortex and the hippocampus, both targets of relevance for cognition affected in AD. Initial clinical findings indicating that patients with treated cholinergic deficiency presented less cognitive dysfunction encouraged the use of PChEI. Clinical trials suggested a delayed progression of symptoms for some PChEI, but the long-term effect continues to be debated.

The first atoms used were physostigmine and galantamine, reversibly inhibiting AChE, with the mechanism of action of the latter including a possible allosteric effect on ACh nicotinic receptors. This is the rationale for today's use of galantamine in symptom relief, as well as of other PChEI used in clinical settings for AD, such as donepezil, tacrine, and rivastigmine.

3.2. Glutamate Modulators

Besides the cholinergic system, impaired glutamatergic transmission has emerged as a central pathophysiological mechanism in AD. Glutamate is the main excitatory neurotransmitter in the brain, important for synaptic plasticity, learning, and memory. Data show that an early and sustained decrease in glutamate levels occurs in the parietal cortex and hippocampus of AD patients. This hypoactivity is responsible for a compensatory over-activation of glutamatergic neurotransmission through NMDA receptors, aimed at restoring physiological levels of synaptic plasticity, and a concomitant increase in the activity of the inhibitory GABAergic system. Glutamatergic overactivity, especially through NMDA receptors, is associated with the enhancement of several neurotoxic pathways, like those activated by Aβ and tau, and mitochondrial dysfunction. In the later stages of the disease, there is a phase of glutamate depletion. In this stage accelerated tau pathology occurs, and the phosphorylated levels of tau correlate with cognitive function, synaptic dysfunction, and neuronal injury. This hypoactivity is responsible for a compensatory over-activation of glutamatergic neurotransmission through NMDA receptors, aimed at restoring physiological levels of synaptic plasticity, and a concomitant increase in the activity of the inhibitory GABAergic system. Activation of NMDA receptors in AD patients can exceed physiological levels not only due to decreased synaptic levels of glutamate but also due to the loss of the synaptic localization of the proteins that regulate local glutamate concentration and the permeability of the

glial cells, which are essential to maintain the spatial buffering of synaptic glutamate. Aβ and tau hyperphosphorylation decrease glutamate uptake by astrocytes, increasing the risk for NMDA excitotoxicity associated with AD neurodegeneration via tau, APP, and APOE.

3.3. Monoclonal Antibodies

Although the neuroprotective and neurodegenerative effects of monoclonal antibodies targeting Aβ may not be solely due to their Aβ clearance properties, the compelling evidence linking Aβ to the onset of Alzheimer's disease has set the stage for the use of monoclonal antibodies as disease-modifying approaches for Alzheimer's disease. Most of the monoclonal antibodies currently available are designed to target aggregated forms of Aβ. Three mechanisms of action may mediate the effects of monoclonal antibodies on Aβ; (i) promotion of the clearance of cerebral Aβ and/or neurofibrillary tangles through blood-brain barrier-opening-induced saturation of the periphery pool of soluble Aβ or Aβ binding proteins; (ii) promotion of the degradation of aggregated Aβ, possibly by brain or peripheral enzymes; and (iii) promotion of microglial-mediated degradation of aggregated Aβ or neurofibrillary tangles, possibly by microglial activation through other mechanisms.

The inconsistency in the clinical efficacy of passive immunotherapies may be attributable to the following: (i) Aβ clearance alone does not allow brain homeostasis restoration on its own; (ii) effects may be detected only in a subgroup of patients; (iii) the early-stage, Aβ-rich period may be much shorter than the disease duration; (iv) the effects on cognition may not be large; and (v) numerous risk factors contribute to the development of dementia in addition to Aβ clearance; none of the latter factors can be addressed through passive immunization. However, many have been prematurely considered to have failed because of the lack of cognitive improvement. Therefore, it is currently believed that monoclonal antibodies targeting Aβ need to be used at the early stage of Alzheimer's disease during which Aβ clearance affects the mini-mental state examination or Clinical Dementia Rating Scale although the early initiation of monoclonal antibody therapy may not guarantee clinical efficacy. Notably, the continuous, aggressive effort to initiate monoclonal antibody therapy in such patients, if effective, would imply a change in the focus of Alzheimer's disease prevention from the evaluation of the preventive effect to the evaluation of Aβ clearance restoration.

4. Emerging Therapeutic Strategies

Alzheimer’s Disease (AD) is a multifactorial disorder with several mechanisms at play, making banking on a single-effect therapeutic strategy impractical considering the different pathophysiological processes seen in AD. Recent attempts have thus focused on targeting a greater array of mechanisms simultaneously, or pharmacological repurposing. The earliest advent of therapeutics focusing on multiple targets utilized rational drug design for the development of compounds with multiple combined modes of action. Lately, however, synthetic biology and the introduction of designer drugs such as nanoparticles, genetic manipulations, viral oleogels, and microinjection methods have seen a rise in popularity.

Amyloid beta (Aβ) has been the focus of many drug discovery initiatives, being a key pathological hallmark in stage 1. Several approaches are taken considering either the generation, aggregation, or clearance of the Aβ peptide. Modulators of γ-secretase were the continuous mode of action therapies developed, with a particular interest in targeting the non-amyloidogenic pathway involving the 40-residue peptide. Solanezumab had been one of the most promising molecules but had since returned with mixed study results. However, challenges remain in ensuring definitive delivery, while a better understanding of microglial activation pathology as well as the recently established role that neuroinflux has in disease progression is driving new efforts into their modulation.

Inhibition of Tau hyperphosphorylation to reduce neurofibrillary tangles is one possible option in countering the progression of stage 1 and preventing the spread of Tau pathology. Possible compounds of research include anti-tau antibodies, transcription factor modulators, tube supervisor agents, protease inhibitors and phosphatase activators, lipid modulation, and anti-inflammation interventions to ameliorate Tau hyperphosphorylation. However, it remains a challenge to ensure clearance of tau pathology, especially in the elderly AD population suffering from normally reduced CNS penetration. However, with the discovery of microglial biology involvement in Tau progression, new avenues of therapeutic discovery are being explored. Targeting neuroinflammation thus remains a current avenue of exploration in terms of the role of the immune system in AD pathology. Certain inflammatory cytokines however may have ambivalent roles in AD pathology, warranting more research for therapeutic modulations. Both ARIA and PAE became hot topics, with potential solutions discussed for the management of ongoing trials.

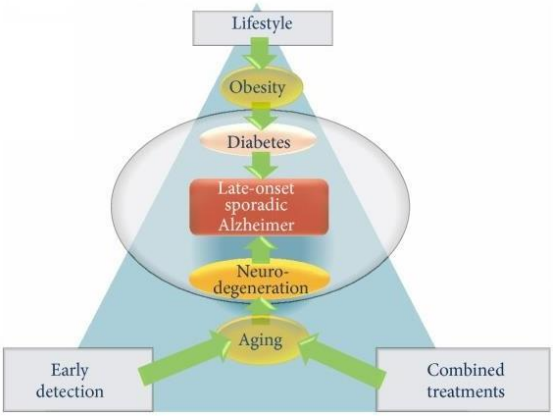

Fig 3 : Current Research Therapeutic Strategies

4.1. Targeting Amyloid Beta

A growing number of clinical trials have tested the amyloid hypothesis of AD by developing an Aβ-targeted treatment. Most of these strategies have focused on reducing the accumulation of the peptide, either through prevention of its production or enhancement of its degradation, to ameliorate the brain deposition of insoluble Aβ deposits. More than twenty anticongophoric treatments aim to disrupt the deposition of insoluble Aβ42 deposits in AD dementia. The majority of symptoms associated with AD have been observed in individuals alive for more than 70 years, not eligible for holes-in-the-head treatments with β-site-cleaving enzyme 1 or γ-secretase inhibitors. Rather, they include at least several dozen immunotherapies, using either Aβ42 vaccines or passive Aβ-ACE, mainly monoclonal antibodies.

Until 2021, the concept that reducing Aβ pathology would result in cognitive benefit had not been demonstrated convincingly in individuals with symptomatic AD. Rather, the majority of Aβ-targeted trials had either failed to achieve cognitive memory advantages or had not been set up to test whether such differences would occur. Moreover, there was a general feeling among scientific pundits that both private and public mass concentration on AD, triggered by funding agencies aiming to stimulate investment in AD therapeutics, had come to the end of a speculative phase in which neither cognitive benefits nor preferential reduction of the abnormal brain biomarkers of Aβ or tau were observed with numerous drugs . In December 2020, despite some controversy about methodology and endpoint, improvement of a cognitive endpoint after 12 months already indicated a favorable risk-benefit ratio, thus paving the path for restarting the second wave of 'Aβ-centered' AD immunotherapeutic trials. Thus, Aβ has returned to the spotlight as a possible target disease-modifying therapy; the question is whether they would all benefit from being returned 'back in time' to hospitalization before their 'acute episode' or whether they would require some sort of symptomatic treatment.

4.2. Tau Protein Modulation

Tau pathology, secondary to hyperphosphorylation, leads to neurofibrillary tangles and loss of synapses and promotes neurodegeneration. Thus, tau therapeutic modulation represents a strategic approach aimed to directly inhibit tau pathology regarding neurotoxic function in Alzheimer's, which for a long time was regarded as a singular tauopathy symptom. After little success with tau monoclonal antibodies, tau modulation is being currently investigated through diverse small molecules in phase I and early phase II trials. By preventing tau protein hyperphosphorylation, tau small molecule inhibitors hold the potential to prevent neuropathological spreading, hence providing benefits to a larger number of patients in more advanced stages of neurodegenerative diseases. The initial promising results for tau inhibitors that prevented tau hyperphosphorylation, arguments favoring tau small molecule inhibitors efficacy, and proposed routes were early neuropathological stage or asymptomatic patients and younger ages of onset of cognitive dysfunction. One of the first candidates demonstrated to be effective in patients with mild cognitive impairment associated with Alzheimer's disease was methylthioninium. Further research troubleshooted confusion raised by the results obtained in tau knockout and tau transgenic models versus observations in tau deficiency animal models, and subsequently proposed tau inhibitors based on tau small molecule actions. A review discussed tau inhibitors and tau modulation strategy roles to ameliorate pathways mediated by the loss of phosphorylation levels causing loss of functions in physiological roles of tau protein involved at microtubule and synaptic activity levels due to alterations implicated in neurodegeneration. Subsequently, based tau modulation actions and tau inhibition mechanisms were reviewed exemplifying their effects on the biosynthesis pathway, tau - proteasome interaction, tau function action, tau aggregation inhibition, and tau gene silencing. Moreover, two phase II clinical trials of usage of the small molecule compound designed to inhibit tau hyperphosphorylation were initiated.

4.3. Neuroinflammation and Immune Modulation

Accumulating evidence from pathogenetic studies suggests that inflammation may trigger and perpetuate the neurodegeneration process, and the immune system may regulate AD development. In this perspective, both innate and adaptive immunity have been implicated in the pathogenesis of AD. The innate immune response, which is mediated by peripheral myeloid cells and tissue-resident macrophages, is involved in Aβ deposition and clearance, as well as in tau pathology, neurodegeneration, neurovascular integrity, and neurogenesis. In the central nervous system, the resident glia forms a specific neuroinflammatory response to Aβ deposition, and the activation of microglia by Aβ, in turn, concurs with neuronal degeneration. On the other hand, aberrant activation of T lymphocytes has also been related to an increased risk of AD, while the functional receptor for Aβ on both microglia and T cells may be the same. Inducible T cell co-stimulator and its corresponding receptor may accelerate neuroinflammation, whereas its negative regulator programmed cell death protein 1 is neuroprotective. Furthermore, controlled clinical trials with specific anti-inflammatory drugs have yielded some interesting results: the long-term treatment of NSAIDs lowers the risk of AD by about 40% to 50%. Recently, Aβ clearance was shown to be augmented by cyclooxygenase-2-inhibiting NSAID, suggesting that inhibition of COX-2 is effective in delaying the onset of AD. In addition, the nonselective COX inhibitors have also shown immunomodulatory effects, mainly by decreasing the production of the proinflammatory cytokines, which are increased in AD. Other studies have revealed that some low-dose NSAIDs help improve cognition in patients with mild to moderate AD. Moreover, new results on the role of the intestinal microbiome in the immune response as well as other modulating immune functions encourage the modulation of the microbiome as a promising new therapeutic strategy against AD.

5. Role of Biomarkers in Alzheimer's Disease

Biomarkers are essential in research and clinical practice for identification, risk prediction, early diagnosis, and monitoring of pathology and treatment efficacy. The term biomarker has been most broadly defined as a defined characteristic that can be measured as an indicator of a normal biological process, pathogenic process, or pharmacologic response to a therapeutic intervention' and can thus be used to represent a natural course of the disease, reflect underlying neuropathology, or indicate response to pharmacologic intervention. Therefore, a variety of molecules, ranging from proteins and lipids to hormones and nucleic acids, could represent biomarkers for Alzheimer's disease, either for the presence of the disease or the underlying alterations associated with the disease. These diverse molecules can be measured in different sample matrices, such as cerebrospinal fluid, serum, urine, or saliva. Importantly, biomarkers from selected sample matrices may provide more accurate disease-related information than others; for example, cerebrospinal fluid biomarkers are measures of the processes occurring in the brain.

1. Biomarkers for Early Diagnosis

Biomarkers are most urgently needed in Alzheimer's disease for early diagnosis, before the onset of clinical symptoms. A growing number of recent studies have shown that the presence of amyloid in vivo detects preclinical Alzheimer's disease in asymptomatic individuals with increased risk for dementia, thus being indicative of preclinical Alzheimer's disease. Furthermore, the temporal succession of amyloid and neurofibrillary tangles is considered to provide the best window of opportunity for intervention. Therefore, CSF or PET biomarkers measuring Aβ42 or amyloid radiotracers must be used for one of the core diagnostic criteria for preclinical Alzheimer's disease. Early clinical trials testing Alzheimer's disease-modifying therapies suggest that treatment should be preventive and started in the transition from a preclinical stage in Aβ-positive individuals, high-symptomatic stage with overt cognitive deficits, influenced mainly by factors like neurodegeneration without significant comorbidity, and the final stage with dementia don't improve untreated clinical outcomes.

2. Biomarkers for Treatment Efficacy

In addition to diagnosis, biomarkers may measure the response to targeted therapies as part of a clinical trial. Phase 2 Alzheimer's disease-modifying trials are ongoing in asymptomatic high-risk individuals using treatments directed at amyloid deposition. These studies use biomarkers as endpoints: the CSF Aβ42 level, PET amyloid tracer binding, and plasma levels of tau phosphorylated at threonine 217 or identified by mass spectrometry are monitored. For trials in symptomatic individuals, the typical endpoints are clinical: the change in clinical presentation, conduct examinations, rates of enrolled individuals responding to placebo or treatment, health-related quality of life, behavior, and neuropsychiatric function.

Equation 2 : Therapeutic Efficacy Score:

$$E_s = \frac{R_c - S_e}{T_d}$$

where:

- E_s = Therapeutic efficacy score
- R_c = Reduction in cognitive decline rate
- S_e = Side-effect severity score
- T_d = Duration of treatment (months)

5.1. Biomarkers for Early Diagnosis

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is becoming ever more frequent and poses a huge burden on public health care due to its permanent cognitive decline. Currently available treatments can only offer partial symptomatic amelioration, leading to a disappointing demand for these therapies. However, the recent development of novel, disease-modifying drugs has raised hopes for better outcomes. Although not curative, they aim at intervening in key pathogenic mechanisms at earlier stages, thus delaying clinical progression. Such a new treatment strategy requires the use of biomarkers, as it is unlikely that clinical symptoms will be detected before these interventions are made. Biomarkers should also help to characterize the disease in a more personalized way, providing evidence for its early, prodromal stages and differential diagnosis from frontotemporal dementia and other dementias. In therapy studies, biomarkers could be used to select subjects that are more likely to respond to treatment.

Biomarkers are biological characteristics that allow the detection of specific pathological processes in living subjects. Ideally, they should be modifiable, i.e., responsive, to treatment. Cerebrospinal fluid (CSF) biomarkers include hypophosphorylated tau and the 42-amino-acid-long amyloid peptide in the prodromal phase, as well as total-tau and tau phosphorylated at threonine-181 in the clinical phase of AD, which are modified during the disease and are related to clinical and neuroimaging progression. CSF biomarkers are useful for differential diagnosis of frontotemporal dementia, in which tau is not increased. However, the invasive nature of the procedures to obtain CSF samples, both lumbar puncture and repeated sampling, limits their utility for widespread screening programs. Moreover, CSF analytes are not expected to reflect the entire range of neuropathological diversity that underlies AD. Therefore, there is an urgent need for the development of novel, not yet validated biomarkers that are easily available through blood samples. Some of these include serum p-tau217 and other modified tau forms, ratios, and neurogranin.

5.2. Biomarkers for Treatment Efficacy

The need to identify treatment-responsive patients is of paramount importance. Biomarkers of disease mechanisms may facilitate patient stratification and allow enrichment for exposure to active drugs. The response may be assessed by longitudinal change and/or dichotomous response as determined by imaging and other methods. Neuropathological research has enabled the identification of ‘active’ processes that likely precede the onset of clinical symptoms. These processes may be directly tested in trials or identified using currently available indirect methods. It may t hen be possible to assess treatment effects with imaging, CSF, or plasma measurements at a single time point in the potentially diseased but asymptomatic and/or symptomatic patient group. CSF or plasma measurements likely reflect the treatment effect more directly and provide a simple, low-cost method to monitor the treatment effect.

Immunotherapy targeting soluble amyloid beta oligomers is currently being tested in a Phase 2 trial in MCI and AD patients. Studies in amyloid mouse models have shown that clearance from extracellular plaques may occur before clinical improvement can be detected. Plasma 40 and 42 levels decrease

and increase, respectively, in patients on active treatment, thereby indicating ongoing plaque clearance in vivo. However, the problem of validating the biomarker concerning clinical response remains. Hence, there is a need to bridge between potential treatment targets identified by neurobiological approaches to those currently available, and to develop AD drugs that modulate such putative pathways; these methods should become as available as testing for phenylketonuria.

6. Translational Research in Alzheimer's Therapeutics

Translational research converts discoveries from basic research into new or better ways to prevent, diagnose, or treat diseases. In this process, the translation of laboratory research into new diagnostics and therapeutics is often defined as moving from bench to bedside. Translational research builds on the research 'pipeline' – a continuum that extends from basic laboratory exploration through animal studies to randomized clinical trials in humans. The recent advances in neuroscience, including the discovery and validation of several novel biomarkers, have allowed the creation of disease targets with greater success in conversion to phase 2 clinical tests. These biomarkers provide information about pathophysiologic mechanisms, identify the appropriate patients for evaluation, and provide biologic measures of disease activity. In addition, we now have better animal models and novel technologies, which can help bridge the gap and allow the exploration of more disease mechanisms in preclinical studies. The disease-modifying clinical trials for Alzheimer's therapeutic interventions can be expensive, difficult to implement, and controversial. These trials need a sufficient size to detect a "meaningful" impact on disease progression and need to focus on an early and homogeneous group of subjects for whom gene and biomarker studies can provide the necessary evidence. Though efforts are being made to improve our ability to test drug efficacy associated with the improvement of cognitive, functional, and global clinical measures, these measures remain still largely subjective. Also, until now, disease-modifying drugs for Alzheimer's disease have not been proven to reduce morbidity or mortality, nor have they demonstrated their efficacy. The current need is to identify relevant new targets and help accelerate the research from bench to bedside.

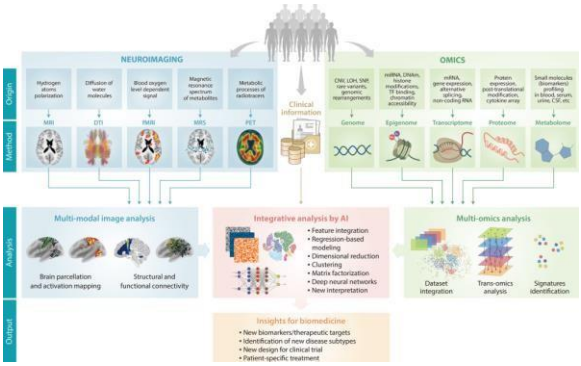

Fig 4 : translational research on the brain

6.1. From Bench to Bedside

Translational research is a bridge between experimental research in animals and cellular models and novel therapeutic approaches in human subjects. Animal and cellular research has become increasingly complex and is based on the development of sophisticated techniques and state-of-the-art models. In particular, cumulative evidence indicates that prion-like spreading of aggregated proteins between neurons and astrocytes is a key mechanism of neurodegeneration. Such knowledge inspired the design of experimental studies using selective immunological, genetic, and pharmacological inhibition of the release of exorphins to test the efficacy of these approaches in animal and cellular models of Alzheimer's degenerating pathology.

Key questions in Alzheimer's translational research are practical ones, such as when to administer a specific treatment and to whom, i.e., what stage of the disease and what age range the specific treatment should be aimed at. Deciding how long and how intensively to treat a pre-symptomatic subject to prevent the emergence of dementia once pathological changes have started in the brain is a very difficult question. Unfortunately, decades-long studies are needed to assess the impact of intervention on the evolution of cognitively healthy subjects or individuals with mild cognitive impairment, which would be economically prohibitive. A transitional solution consists of using cognitively healthy subjects or patients with mild cognitive impairment who harbor Alzheimer´s disease biomarkers for enriched studies. Indeed, the presence of established neurodegenerative changes in cognitively healthy subjects with genetic at-risk factors allows for performing studies with a more limited time frame than population studies, therefore addressing the issues mentioned above in a more practical manner than population studies.

6.2. Clinical Trials and Their Challenges

While basic science is critical in understanding the underlying mechanisms of the disease and identifying drug-able targets, it will be the clinical trials that validate the hypotheses and determine whether indeed there is a fruitful therapeutic path to pursue. As basic scientists do their work, they must continuously translate their findings into clinical investigations and advocate for trials that test their most innovative ideas. Clinical research is not only about testing putative drugs, it encompasses a broad spectrum of activities, establishing preclinical and clinical biomarkers, developing risk modification strategies, and testing drugs for their potential disease-modifying, symptomatic, or risk-modifying potential. Today, with the increasing interest in Alzheimer's Disease from the biotechnology and pharmaceutical industry, several ongoing clinical trials are based on a sound scientific rationale. Other trials, however, are criticized for being too ambitious or too flawed and fail to define the proper targets and a scientific rationale, to select the correct population, or to incorporate the appropriate experimental designs. These imperfections can stem from the complexity of the disease, the numerous

aspects that are still poorly understood, and the relatively high costs that pharmaceutical companies must make to optimize their odds of success. When AD entered the drug development pipeline, only a handful of companies initiated their attempts, when demand was relatively low.

7. Patient-Centric Approaches

Consumerism in healthcare has prioritized patient-centered approaches; however, implementation of these concepts is often lacking. For many clinical trials in AD, patient feedback on device preferences, symptom burden, and function performance is not captured, and objective measures may not correlate well with patient self-reports or caregiver reporting. Moreover, endpoints selected by sponsors may not take into consideration real-world considerations such as safety and tolerability concerns or treatment burden. Strategies for optimizing feedback from AD patients, family members, and informal caregivers should both follow general best practices for research in vulnerable populations while also considering the unique cognitive, behavioral, and functional capacity changes that often accompany dementia. Such considerations will benefit both the research and regulatory communities in understanding patient needs and input for clinical trial design and device development. Increasingly, clinical outcome assessment guidance is encouraging the inclusion of function and quality of life, especially for conditions that are not acute. Moreover, contemporary thinking endorses employing the least restrictive informant or respondent, which could be the investigator, the caregiver, and informant, or the patient. In addition to general longitudinal changes in cognitive function, researchers should consider screening for safety and tolerability with structured interviews of people living with dementia or AD, either informally or with family and loved ones. Pragmatic and flexible engagement with patients and caregivers regarding perceptions, experiences, and evaluations of potential treatment effects using COAs could enhance both implementation feasibility and acceptability and optimize the relevance of real-world impact. Some recent guidance encourages researchers to include relevant non-participant stakeholders, as consensus amongst community groups and societies may improve the COA relevance and impact.

7.1. Incorporating Patient Feedback

Public and patient involvement (PPI) in research is essential to ensure that priorities in research reflect the needs of patients. This is especially true for dementia: the clinical heterogeneity in presentation, symptom burden, level of disability, and care needs means that there is genuinely no one-size-fits-all approach for patients. Traditional pharmaceutical research is often bespoke and disconnected from the patient experience but more recently, PPI has originated in large drug company networks, developing a blueprint for deep patient connections. Ensuring that proxy measures are good predictors of efficacy and side effect burden in the key dementia phenotypes is critical, just as agreeing on a consensus for drug duration for trials in presymptomatic patients is vital.

In dementia, as in any age-related disorder, the relevance of the discovery of a putative target is dependent upon what the drug will do, be it the clinical modification of the disease by delaying onset, progression, or reducing co-morbidities or the prevention or treatment of the underlying cause in those more afflicted. In many conditions, the response is measured by clinical ratings; for example, by the assessment of experts in a particular field or by the patient or family being asked to answer questionnaires at various visits to the clinic. In developing a new drug, we must answer two locally important questions. Among the many potential clinical outcome assessments available for exploration, which will be most sensitive and feasible for our patients initially, for long-term studies in those more affected, as well as the presymptomatic and presymptomatic-mildly affected patients? Then, if we show success in phase 3 trials, do the results transfer to meaningful practice for patients in the outside community?

7.2. Quality of Life Considerations

Across the continuum of dementia and Alzheimer's Disease, the clinical trajectory of individuals may vary widely, and in any given individual, clinical features may wax and wane. These variations occur in many different dimensions, including cognitive, emotional, behavioral, functional, social role, nutritional, medical burden, and physical health. Many of these changes can substantially increase the burden on caregivers and others but do not have an objective measure, detectable treatment effect, or valid endpoint for therapeutic trials. While any one of these proposed endpoints is likely to be partially correlated at best, multidimensional assessments can characterize the unique individual experiences and circumstances of those with Alzheimer's Disease and dementia, focusing on those changes that may be specific to one particular illness. An understanding of the diverse quality-of-life experiences of people living with Alzheimer's Disease related to both the disease and the impacts of treatment with best-informed clinical care decisions and aid in the design of clinical trials, risk/benefit analyses, and regulatory issues. To obtain and accurately describe the diverse quality-of-life experiences of those living with Alzheimer's Disease, it is important to also be sensitive to these potential individual differences and to assess the ability of Alzheimer's Disease patients to participate in and engage with survey items.

Surveys can serve a purpose beyond clinical staging and can lend important insights into the individual preferences of people with Alzheimer's Disease who may be at different stages of disease when making decisions about any therapy. Detectable effects are often only seen with advanced disease, but the natural history of diseased and non-diseased individuals must be taken into account. Proxy reports by caregivers or health care professionals are also affected by their particular circumstances and can be inaccurate, especially when patients are reasonably able to respond directly. Finally, developing a more complete knowledge of the quality-of-life dimensions relevant to patients with Alzheimer's Disease and dementia creates the opportunity to improve medical treatment and both non-pharmacological and social interventions.

8. Future Directions in Alzheimer’s Research

Even though countless molecules have been identified as targeting the pathological features of AD and have been tested in affected populations, very few of them have progressed to clinical use. For this reason, drug development in AD is still challenging. New AD therapies, including AD vaccine strategies and other ancillary agents, need to be more extensively tested before they can be extensively applied in patients. In preclinical and clinical AD studies, potentially efficacious therapeutic strategies must simultaneously consider the distinguished sex-specific and multi-faceted nature of the

disease. Hence, strategies to target different mechanisms at different stages and use combinations in selected populations are likely to be the future of AD therapy. Furthermore, localized and selective drug delivery can help to overcome problems of the blood-brain barrier. For peripheral delivery of AD therapeutics, several innovative drug delivery systems have been developed that include directed drug delivery, sustained drug delivery, and nanoparticle drug delivery. Ultimately, several unanswered questions in AD remain. Successful therapeutic interventions in AD will require that the complex and multi-faceted nature of the disease is first completely understood. Small clinical studies to clarify the built-in complexity of the AD population are of utmost importance. These may serve to guide future larger studies that utilize novel multi-targeting combinations tailored to the individual patient. To this end, the future of AD research must rely on multidisciplinary research teams that truly bridge basic with clinical and pharmaceutical AD research. Indeed, the integration of neuroscience, establishment of age- and sex-associated molecular biomarkers, heterogeneity-based precision medicine approaches, targeted research applied to advanced model systems, and the development of effective therapeutics working along the lifetime window of AD pathogenesis are currently new challenges.

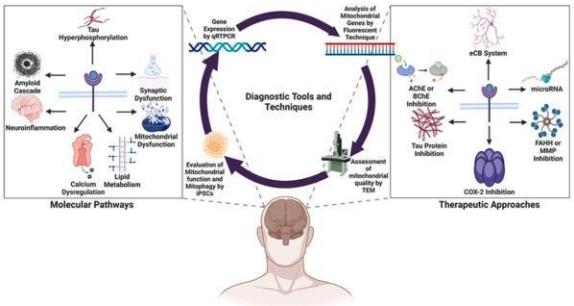

Fig 5 : Alzheimer's disease

8.1. Innovative Drug Delivery Systems

Therapeutic doses of potentially effective BH4 supplements, such as sapropterin, for mild cognitive impairment and early stages of AD, have largely been determined in animal studies. These doses will not work in humans, as the compound has been proposed to minimize dose-related complications, adverse drug reactions, and reactions associated with chronic high-dose BH4 therapy via a feedback mechanism, that is, the promotion of excretion of excess BH4 in urine, but only in patients with severely impaired BH4 metabolism. Presumably, normal levels of BH4 metabolism would allow for the accumulation of adequate amounts of functional BH4 despite the ongoing BH4 supplementation. Hence, to validate findings on the one hand and to design adequate clinical trials on the other hand, preclinical studies in animal models that closely resemble the particular features of the target patient population are warranted. Invasive systems and/or novel formulations of BH4 are being developed for relatively non-invasive systemic use to target the CNS. This increase in the potential therapeutic options for patients with AD has been made possible by the gradual unraveling of the various neurochemical alterations associated with AD. Further validation of the findings and optimization of the novel therapies, especially regarding their efficacy, require extensive longitudinal studies in well-defined, homogenous patient cohorts that enable subtype classification. In addition, the implementation of known therapies with established efficacy in blood and vascular disorders, whether or not with a mode of action in common with BH4, in patients with specific AD subtypes may also help to ameliorate the forecasted expansion of this devastating decline of human cognitive abilities.

8.2. Precision Medicine Approaches

Targeting the right therapeutic at the right stage of disease and the right target will significantly improve the odds of success in clinical development and decrease both the risk of financial wastage, but also, most importantly, the risk of exposing patients to ineffective and potentially harmful drugs. As knowledge about the pathophysiology of Alzheimer's disease expands, particularly about the dysregulation of different cellular and molecular pathways, it is anticipated that there will be a growing impact of precision medicine approaches on the clinical development of therapeutics for AD. Furthermore, with current advancements in target validation and drug discovery, and the increasing availability of metabolites and molecular profiles at early diagnostic and prognostic stages of the disease, the era of precision medicine for AD drug development will soon be upon us. Several translational research approaches are needed in this instance, including the adoption and design of novel clinical trials, studies on metabolites, AI-assisted biomarker discovery and validation, surrogate endpoints, and complex disease modeling. The use of disease stratification approaches in clinical trials can increase their power, size, and success rate. By assessing mechanisms that link genotype with phenotype, we can identify groups of patients who respond to a specific drug or a group of drugs targeting the same underlying disease process. Such a drug would likely be ineffective or reduce a disease-associated biomarker without clinical benefit in non-target genetically defined subjects. Disease stratification based on the pathophysiological understanding of the pathways regulated by the encoded proteins of genetic variants typically detected in disease-modifying AD genes is already informing clinical trial planning and design. Such trials target the use of specific anti-AD drugs in subjects genetically defined by rare highly penetrant variants. There is growing interest in a deeper understanding of the role that genes associated with neuroinflammation, lipid metabolism, synaptic plasticity, neurotransmission, and more recently autophagy, play in non-symptomatic AD patients and how this relates to the symptomatic disease. These studies are likely to be based on novel insights into AD clinical staging and the development of precision medicine.

9. Ethical Considerations in Alzheimer’s Research

A wide array of ethical issues arise when studying Alzheimer’s disease, particularly in interventional clinical trials. The presence of significant cognitive impairment in many affected individuals casts doubt upon their ability to provide informed consent. Access to care and participation in clinical studies

should not be limited only to subjects with adequate cognitive capacity to provide consent independently; consent can instead be facilitated by the implementation of special procedures and safeguards that allow additional close family involvement.

Consensus guidelines identified these special circumstances and presented guidance for the use of different consent models to enhance subject protection. These include shared decision-making and the use of a legally authorized representative for individuals deemed incapable of providing informed consent. Despite extensive prior efforts to recommend procedures for obtaining informed consent in clinical studies, the approach to the issue remains inconsistent at best, and the high prevalence of incapacity among subjects is widely acknowledged. It is estimated that only 36% of cognitively impaired subjects can provide independent consent, meaning that more than half will require their decision-making capability to be supplemented by a family member or use a legally authorized representative. Dampening consent capability further, Alzheimer's disease is associated with abnormalities in affective cognition that impair emotional decision-making.

Consequently, the majority of subjects enrolled in clinical trials are usually accompanied by family members in the decision-making process regardless of their ability to provide informed consent independently. Furthermore, family involvement is particularly prevalent when the subject is in a capacity assessment range associated with the lowest likelihood of adequate consent capability. Finally, while recognized as an important protective measure for individuals whose capacity to consent is in question, legislation concerning the use of legally authorized representatives is not uniform across the world.

9.1. Informed Consent Challenges

Informed consent is an imperative part of the standard ethical practice that assures the autonomy of patients when they agree to participate in clinical trials. Fundamental to informed consent is the notion that individuals have the right to make decisions about their own bodies and medical care. Patients must be able to participate in research and make their decisions known if they choose to do so. Informed consent could also be viewed as a legal instrument that can protect the rights and interests of both patients and researchers or policymakers, although these parties have very different interests. Informed consent and communication of what research entails between the participant and researcher is especially important in the research field. Legally, informed consent describes the procedures by which patients provide permission for procedures to be carried out, or for biological specimens or medical data to be stored for future use. Broad consent typically applies to the use of information or materials that comply decades after the original acquisition and generally covers use for diverse purposes of widespread public benefit. Informed consent may lack effectiveness when the patients' cognitive faculties have been impaired by neurodegenerative diseases, and even with the presence of caregivers or proxies. The fact that many patients have impaired capacity, or varying levels of capacity or fluctuating capacity, creates challenges for investigators when obtaining informed consent. Considering the structure of how informed consent is currently applied, a large group of dementia patients are involved in research studies. While the ethical obligation of facilitating autonomy is laudable, it is infeasible to abandon enrollment entirely in comparative-effectiveness studies because the ability to provide valid informed consent is absent.

Equation 3 : Clinical Trial Success Probability:

$$P_s = \sigma\left(\gamma_1 B_e + \gamma_2 S_s + \gamma_3 P_s\right)$$

where:

- P_s = Probability of clinical trial success
- σ = Sigmoid activation function
- B_e = Biomarker effect size
- S_s = Symptom stabilization score
- P_s = Patient stratification quality
- $\gamma_1, \gamma_2, \gamma_3$ = Weighting factors

9.2. Equity in Clinical Trials

Ensuring equity in trial design and implementation is critical to improving both individual outcomes and the generalizability of clinical trials. It is possible that diverse and historically underrepresented groups have higher rates of Alzheimer's Disease and other dementias but do not have equal access to educational resources, prevention strategies, and clinical trial opportunities. Racial and ethnic groups vary in important dimensions that could influence risk and neuroprotective strategies. The details of individual and community-level risk factors, such as exposure to chronic stressors, diet, socioeconomic status, general health status, medical comorbidity, access to preventive care, and level of CAA could contribute to disparities between demographic groups. Furthermore, high-profile violations of trust have eroded the credibility of the medical system and academic institutions' relationships with minority communities. Researchers must build relationships of transparency and reciprocity by including community representatives in the study design process, ensuring that the trial will benefit participants and the larger community, and using community representatives to assist with recruitment and retention.

Publishing and discussing considerations of trial design beyond the actual execution may allow for future advances guided by community input and consideration of community factors. There is a growing movement for investigators from underrepresented backgrounds to be a part of study design, recruitment, retention, and dissemination efforts. In Alzheimer's Disease Research, all stakeholders must identify an intervention of importance to the

specific community and educate that community on the study design. More importantly, we must implement strategies that accomplish recruitment and retention of community participants to assess the impact of factors unique to a community on trial-specific outcomes.

10. Global Perspectives on Alzheimer's Disease

The world, through scientific collaboration and technological advances, has accelerated the discovery of causes and risk factors for Alzheimer's disease and other areas of neuroscience research. Whether addressing pathways for genetic discovery, exploration of pathological mechanisms that are shared with each area, the effects of comorbid medical and psychiatric problems on clinical expression and development, population-based studies of risk and protective factors, studies that use postmortem tissue or animal models, or discovery of biomarkers for genetic or biological risk, progress in Alzheimer's disease will be strengthened by collaboration and sharing of tools and results that together promote positive translational results, from core scientific discovery to direct applications that benefit patients, patient's families, and ameliorate burden of health systems. Studies at the population level require collaborative efforts in which large sample sizes from diverse groups can be assembled, with harmonized data structures that allow the pooling of data. These studies examine genetic and biological markers, sex and gender effects, and psychosocial risk/protective factor effects, along with clinical outcomes. Such an effort will also require collaboration with the pharmaceutical industry to ensure that employees who give so freely of their genetic and biological material can be assured that the results of the research will benefit the entire population, promoting the development of new treatments for all therapies that allow hopes of development of curative or preventive therapies to be tested. As our understanding of the complex etiology of Alzheimer's disease emerges, it is increasingly clear that more and more discoveries relate to biological pathways which are also related to other fields of investigation.

10.1. International Research Collaborations

Collaborative efforts that bring together multinational and multidisciplinary investigative teams to address a common research question are the hallmarks of global biomedical research today. These innovative models have advanced our understanding of stroke, tuberculosis, HIV, and cancer, among others, and are beginning to enhance our understanding of other neurodegenerative disorders, such as Parkinson's disease. Although AD research has typically progressed on a more geographically focused basis, generally reflecting the location of the AD expert, there are early programs directed toward international collaboration that yield exciting results. Several other models are emerging that may allow for more AD sites to get involved. Programs allow countries and sites that have historically under-enrolled in AD clinical trials to participate in the discovery and validation phases of biomarker research. Initiatives have recently implemented similar approaches aimed at including more Alzheimer's disease innovative biomarker study sites.

What are the primary reasons for the relatively low levels of international collaboration in Alzheimer's disease research? The aging societies of the Americas and Asia have invested historically considerably fewer resources into basic and clinical AD research than Japan and the European countries. As a result of the low levels of funding, fewer opportunities exist for expanding the investigator base in the Americas and Asia. As such, the requisite infrastructure to permit consolidation of resources and expertise to create the large numbers of well-characterized AD patients that are necessary to allow for the identification and validation of new AD biomarkers either do not exist or exist on a much smaller scale than those networks currently funded in Japan and Europe. Hence, there are no AD research centers of excellence that have large numbers of experienced investigators, specialized staff, and a large influx of patients.

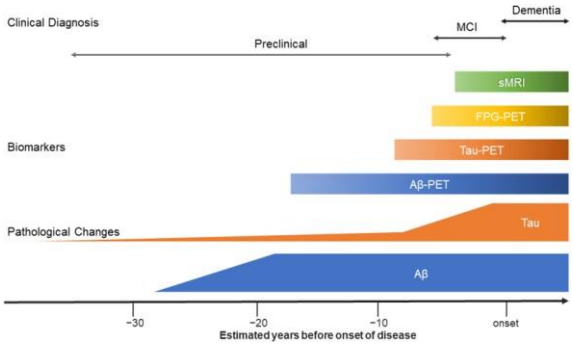

Fig 6 : The Alzheimer's disease continuum with corresponding

10.2. Public Health Strategies

As populations age, potentially higher numbers of individuals will enter the symptomatic periods for late-onset AD, emphasizing the need for effective public health policies. Such policies should also indeed begin during middle age when the preclinical changes of AD appear. Focusing on the modification of the numerous AD risk factors has the potential not only to reduce greatly the expected suffering with dementia but also to reduce the percentages of affected individuals in nursing homes and other health- and cost-intensive services.

It is important to clarify what these favorable public health policies should entail. First, they should focus on the general population as well as on individuals: the general population means health promotion strategies to generally reduce the undeniable importance of modifiable risk factors for AD such as hypertension, smoking, depression, sedentary lifestyle, high blood cholesterol, and diabetes, which can be pursued with implementation of public health measures to improve nutritional intake and increase education and physical activity level. These general efforts should take place even before the risk factors appear since the effects of demographically visible hypofertility as well as of increasing life expectancy of the healthiest

individuals are already observable. These changes are modifying the demographic transition curve and the associated age structure of populations, with a proportionally larger increase in the adult oldest age groups.

11. Conclusion

Alzheimer's disease (AD) represents a major unmet medical need, as the rapidly expanding number of patients with this condition are generally poorly served by available therapies. Clinical trials have thus been directed primarily towards the use of agents that address one of the current theories of pathophysiology, particularly the amyloid cascade. More recently, however, the field has made concerted efforts to explore other potential therapeutic modalities, which both bridge basic laboratory research to potential clinical translation and might be more efficacious methods of delivering better therapies. These include repurposing existing agents, stimulating neural repair mechanisms, using novel vaccines and immune system modulators, identifying novel pathways related to AD pathophysiology, and improving neurotransmitter deficits with the use of novel combinations and approaches. Addressing the interaction of various disease risk factors and comorbidities with AD pathology, particularly in its early and prodromal phases, might also facilitate better therapy and trial design. Overall, there is considerable optimism that with these new modalities at hand, we can avoid the fate of prior trial failures and improve outcomes for future patients.

Increased research investment has enhanced our understanding of both the biological basis for AD and the potential for novel therapeutic strategies. Bridging new biological discoveries and related upcoming clinical strategies can represent a key factor for success in the delivery of better therapies to the increasing number of patients with this condition. In particular, we can no longer afford to pursue unidimensional approaches based on current aging-associated models. Instead, we need to adopt multidimensional schemes that link the patient to the biological basis of their clinical expression of disease. Within such a framework, we would promote a more precise identification and earlier approaches to people at risk for accelerated cognitive decline. In this context, the joint activities of biobank initiatives and academic-industry partnerships represent a unique opportunity to guide the investigation and development of promising new AD therapeutic avenues.

11.1. Summarizing Key Insights and Future Considerations

Recent groundbreaking studies have shed light on the multifaceted pathology of Alzheimer's disease (AD), prompting researchers to rethink the potential for neuroprotection in this devastating form of dementia. Current therapeutic strategies that are most advanced in clinical development focus on the selective inhibition of tau hyperphosphorylation and neurotoxicity. Biochemical and preclinical evidence support the concept that a neuroprotective add-on therapy will be required to limit disease progression, in the light of clinical observations which suggest that current anti-amyloid therapies will not be sufficient to prevent cognitive decline. However, the failure of previous neuroprotective strategies and the lack of structural knowledge on how the major tau kinases and phosphatases interact with downstream tau phosphosites have made the establishment of brain-targeted inhibitors and/or stabilizers of the tau dephosphorylation process a big challenge.

Nonetheless, recent advances in structural and small molecule design permit us to envision a more realistic scenario for targeted neuroprotective strategies, which would act synergistically with other AD therapeutic strategies or be used to address a residual neurodegenerative process after anti-amyloid/anti-tau treatments. It is conceivable that by intervening in the neuroinflammatory processes leading to cholinergic deficits, tau hyperphosphorylation, and neurotoxicity, promoting some degree of neurogenesis, neuronal survival, or mitochondrial function, we would be able to limit the relapse in cognitive deficits. While novel therapeutics targeting tau hyperphosphorylation, tau phosphatase, and tau neurotoxicity are in advanced clinical trials, preventive measures or add-on therapies focusing on tau pathophysiology should be developed, based on previous lessons, in parallel with preventive or curative strategies targeting Aβ. This review will summarize the different classes of therapeutic strategies targeting tau and discuss what the major bottlenecks in the field are.

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