Unlocking the mystery of Alzheimer's disease: Controversies over hypotheses

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The year 2012 represented to be a crucial year for Alzheimer's disease researchers, with the failure of the two most promising drug candidates in phase III clinical trials, namely bapineuzumab and solanezumab that were based on the beta-amyloid hypothesis, which has traditionally been the dominant focus of research and development in Alzheimer's disease. Although there have been several such beta-amyloid based product candidate failures in the past, which include Flurizan from Myriad Genetics Inc., semagacestat from Eli Lilly, Ponezumab from Pfizer Inc., to name a few, the recent discontinuation of these two pivotal phase III clinical trials have raised serious concerns among companies regarding the 30-year old beta-amyloid hypothesis. This has not only led to the disappointment of researchers, patients, governments and investors, but has also lowered the confidence of the smaller companies with pipeline candidates targeting beta-amyloid, to proceed further with their clinical trials.

Given the rapidly expanding patient population, significantly huge economic and emotional burden to patients and family members and unproven long-term benefits of existing drugs, next-generation disease-modifying therapies are the need of the hour. Perhaps, resorting to the second hallmark feature of Alzheimer's disease, namely tau protein, which has been gaining increasing attention in recent times, could open up new opportunities. Nevertheless, several other controversial disease-modifying hypotheses have been postulated to unlock the mystery of this complex disease.

THE BETA-AMYLOID MECHANISM – WHAT WENT WRONG?

Although at investigational level, disease-modifying drugs on successful completion of

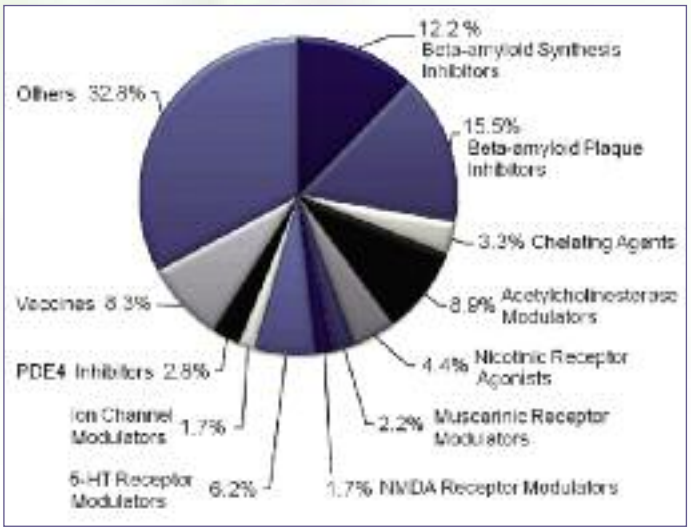

Figure 1 – Alzheimer's disease medication market: Per cent of drug candidates in pipeline by mechanism of action, Global.
Others include AMPA receptor agonists, H3 receptor agonists, sigma receptor agonists, and neuroprotective and neurotropic compounds. All figures are rounded. The base year is 2012. Source: Frost & Sullivan analysis.

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clinical trials are likely to set a new industry standard owing to their specificity, greater therapeutic efficacy, less side-effects and ability to delay or arrest disease progression rather than offering mere symptomatic benefits. With more than 230 drug candidates at various stages of the clinical pipeline for Alzheimer's disease, it is alarming to note that drugs targeting beta-amyloid constitute 27.7% of the total drug candidates in pipeline as of 2011 (Figure 1). Beta-amyloid based drugs can be primarily classified into two types based on their mechanism of action namely beta-amyloid synthesis inhibitors and beta-amyloid plaque inhibitors.

Beta-amyloid Synthesis Inhibitors

Beta-amyloid, produced on/after proteolytic, sequential cleavage of the amyloid precursor protein (APP) by beta and gamma secretases, is the hallmark feature in the pathogenesis of Alzheimer's disease. Hence, the amyloid synthesis inhibitors are primarily of two types, namely beta secretase/BACE inhibitors and gamma secretase inhibitors.

Beta Secretase/ BACE Inhibitors

Only a small portion of the APP undergoes proteolysis by the BACE inhibitors in an amyloidogenic pathway. Although it showed promising therapeutic effects in animal models, identification of small inhibitors for drug development poses challenge. Vast majority of the compounds are in the pre-clinical phase, with very few in phase I stage.

Gamma Secretase Inhibitors

Gamma secretase is a high molecular-weight complex protein, acting on the cleavage products of alpha and beta secretases, leading to the production of beta-amyloid. Gamma secretases act on multiple substrates, especially N-cadherin and notch, and the inhibition of this enzyme could induce toxicities, owing to their direct impact on notch-signalling pathway. Hence, development revolved around second-generation gamma secretase inhibitors which do not influence notch-signalling pathways.

Semagacestat (LY450139), a gamma secretase inhibitor from Eli Lilly, being studied as a potential anti-Alzheimer therapy in two phase III trials namely IDENTITY and IDENTITY2, was withdrawn in August 2010. The interim analysis of the two phase III trials showed that Semagacestat was unsuccessful in delaying disease progression and was associated with worsening of clinical measures of cognition and ability to perform activities of daily living as compared to placebo. Additionally, there was an increased risk of skin cancer in patients treated with Semagacestat as opposed to those treated with placebo.

Flurizan (tarenflurbil), a selective amyloid lowering agent, from Myriad Genetics was one among the first few disease-modifying drugs to reach phase III clinical trials. The drug was known to selectively modify gamma secretase enzyme activity to bring about a conformational change in the amyloid precursor protein, thereby producing non-toxic beta-amyloid (A-beta) fragments, namely A-beta 38 and A-beta 40. Thus the toxicity of A-beta 42 was reduced. However, a phase III trial conducted in 2008 showed that Flurizan failed to produce statistically significant results in improving cognitive abilities of patients as compared to placebo, which forced the company to discontinue the drug development.

Despite these unfavourable results, there are a handful of companies developing gamma secretase inhibitors, which include Bristol-Myers Squib (avagacestat), Merck (MK-0725), EnVivo Pharmaceuticals (EVP-0962) and a few more.

Beta-amyloid Plaque Inhibitors

This mechanism focuses on two important aspects of Alzheimer's disease, which include beta-amyloid plaques – a reservoir of beta-amyloid that can diffuse and cause tau phosphorylation over the course of several years; and aggregated A-beta 42 – a potent stimulator of microglia and the subsequent chronic inflammatory reactions. Most of the amyloid plaque inhibitors function based on antibody technology. It is important to facilitate beta-amyloid clearance due to the neurotoxicity of soluble A-beta 42.

Bapineuzumab, the blockbuster humanized monoclonal antibody, co-developed by Pfizer and Johnson & Johnson, failed to meet its primary efficacy endpoint in its Phase III clinical program in mild-to-moderate Alzheimer's disease patients in August 2012. However, the drug showed positive results in lowering CSF total tau and phosphorylated tau in brain imaging and spinal fluid analysis. Likewise, Eli Lilly's solanezumab, quite similar to bapineuzumab, also failed its phase III trial, EXPEDITION in the third quarter of 2012. The failure of these two much-hyped blockbuster drug candidates has re-emphasized the fact among researchers that a patient diagnosed with mild-to-moderate Alzheimer's disease has already been subjected to several years of brain damage and initiating the treatment at an earlier stage, particularly in high risk groups and those with Mild Cognitive Impairment could have beneficial effects. Gantenerumab and Crenezumab from Roche Holding AG are other monoclonal antibodies being evaluated in Phase II trials.

Currently, the only active phase III clinical program for Alzheimer's disease includes Baxter International Inc.'s Gammagard Liquid (Immune Globulin Infusion (Human) 10%, wherein patients are being evaluated for a 18-month therapy course, in order to prove Gammagard's long-term benefits over a period of three years. Intravenous immunoglobulin (IVIg) therapy, which involves the administration of natural anti-amyloid antibodies obtained from the plasma of healthy donors to Alzheimer's disease patients, is considered to reduce beta-amyloid levels in the brain, improve cognitive abilities and act as a potent central nervous system anti-inflammatory agent. However, owing to its blood-based nature and restricted supply, Gammagard therapy is expected to be more expensive ranging between $ 3,000 and $ 6,000 per dose, depending on the patient's body size.

TAU THEORY – A NEW GLIMPSE OF HOPE

Such unresolved controversies on-going with beta-amyloid and apprehensions among smaller pharmaceutical companies working on beta-amyloid to progress their phase II clinical trials to Phase III, has driven the second hallmark feature of Alzheimer's disease, namely tau protein, to limelight. Tau is an axonal protein that promotes the assembly and stability of microtubules in healthy neurons and its phosphorylation is regulated by kinases such as GSK-3 beta and CDK-5, as well as phosphatases. The hyper-phosphorylation of tau, thought to be induced by soluble amyloid-beta 42, leads to neurodegeneration by microtubule disruption, and the resulting neurofibrillary tangles block neurotransmission and axoplasmic transport.

The overwhelming interest on beta-amyloid for the past 30 years has resulted in the negligence of tau proteins. However, few companies strongly believe that rectifying tau abnormalities could be the key to slow down or reverse symptoms of Alzheimer's disease. Currently, three companies are active in this space and one of them, namely Noscira S.A has a drug candidate, Nypta® (tideglusib; NP-12) based on GSK-3 inhibition, in Phase II clinical development. GSK-3 has emerged as a novel, highly promising therapeutic target for Alzheimer's disease, owing to its involvement in the two main biochemical pathways underlying the neurodegenerative process, including tau

hyperphosphorylation, amyloid formation, amyloid-induced toxicity, synaptic plasticity and neuronal survival.

Allon Therapeutics Inc. is currently evaluating its lead compound, davunetide, derived from a naturally occurring neuroprotective brain protein, activity dependent neuroprotective protein (ADNP) that inhibits tau aggregation in Phase 2a clinical trials. Following the intolerability of the highest dose of its first-generation tau aggregation inhibitor (TAI), rember™ (methylthionine chloride), in an international Phase II clinical trial in mild-to-moderate Alzheimer's disease patients, TauRx Pharmaceuticals Ltd., a Singapore-based company, is currently investigating its second-generation TAI called LMTX under a U.S Investigational New Drug. Both Allon and TauRx are likely to advance their studies to the Phase III clinical program in 2013.

OTHER DISEASE-MODIFYING THEORIES AND THEIR UNDERLYING MECHANISMS

In addition to the above two most widely pursued drug classes targeting beta-amyloid and tau protein, several other hypotheses have been put forward by researchers based on the mechanism of action of different disease-modifying drugs, which are as follows.

Nicotinic Acetylcholine Receptor Agonists

One of the key areas of focus in AD is the deficiency in cholinergic neurotransmission owing to the selective loss of cholinergic neurons and nicotinic acetylcholine receptors (nAChR) in the hippocampus, which influences the cognitive performance of an individual and offers neuroprotection against beta-amyloid-induced cytotoxicity. Stimulation of these receptors are considered to improve cognitive impairment in AD patients and counter the losses of synapses and neurons.

Muscarinic Receptor Modulators

Majority of the amyloid precursor protein (APP) is processed by the alpha-secretase enzyme in a non-amyloidogenic pathway. Muscarinic receptor agonists are considered to trigger this non-amyloidogenic cleavage of APP, resulting in reduction of beta-amyloid levels. Thus, muscarinic receptor agonists find potential application not only in the symptomatic treatment of AD, but also influence the progression of the disease.

5HT (Serotonin) Receptor Modulators

It is hypothesized that the loss of serotonergic neurons not only leads to cognitive disruption, but also behavioural symptoms like anxiety, depression and insomnia. However, there are seven major classes of 5HT (serotonin) receptors and it is not yet clear as to which receptor sub-type needs to be inhibited or stimulated to improve cognitive or behavioural symptoms in AD patients. The 5-HT(4) and 5-HT(6) subclasses are extensively studied, as agonists of these receptors are considered to enhance memory, cognition level, and behavioural symptoms in AD patients.

Ion Channel Modulators

It has been hypothesized that the dysregulation of calcium homeostasis is likely to play a crucial role in accelerating some of the pathological processes in AD. Interestingly, the underlying biochemical events, such as activation of calcium channels, disruption of intracellular calcium stores and subsequent production of free ions by calcium-sensitive enzymes lead to neuronal death in AD patients. The critical function of calcium signalling is backed by two facts. Firstly, mutated presenilins, in patients with familial history of AD it facilitates beta-amyloid generation due to the elevated cytosolic calcium concentration. Secondly, the molecular mechanism of the already approved memantine aids in prevention of excessive calcium influx via the NMDA receptor-mediated ion channel, thereby protecting the cells from glutamate toxicity and dying.

Chelating Agents

It is believed that amyloid-beta aggregation is partially dependent on metal ions, such as copper and zinc. This is based on the fact that A-beta 42 can be precipitated by zinc and radicalised by copper, and both the metals are significantly accumulated in plaques. Therefore, Cu/Zn chelating compounds are anticipated to induce A-beta 42 solubility and prevent plaque formation.

Phosphodiesterase (PDE) 4 Inhibitors

Phosphodiesterase inhibitors help in the prolongation of cyclic Adenosine Monophosphate (cAMP) signalling, that plays a key role in regulating memory and enhancing cognitive performance by counteracting deficits in long-term memory, as a result of over-expression of mutant forms of APP. Additionally, PDE 4 inhibitors are known to offer neuro-protective, neuro-regenerative and anti-inflammatory effects.

Vaccines

Vaccines engage in active or passive immunisation of AD patients with fibrillar amyloid-beta, resulting in the production of anti-amyloid antibodies. This mechanism has been explained by two hypotheses. Firstly, antibodies are considered to bind amyloid plaques and trigger amyloid-beta aggregation by microglia. Secondly, circulating antibodies may bind soluble amyloid-beta in the periphery, thereby causing an amyloid-beta efflux from the brain, commonly referred as the "peripheral sink hypothesis".

Others

Others include drug classes that are developed only by a very few companies. They are AMPA Receptor Agonists, H3 Receptor Antagonists, Sigma Receptor Antagonists and other Neuroprotective and Neurotropic compounds. Furthermore, the mechanism of action for nearly one-third of the compounds in pipeline could not be exactly identified, which reflects the complexity of the disease pathology and underlying mechanism.

CONCLUSION

Therefore, such high levels of associated complexities and high failure rate (nearly 92%) of clinical compounds, makes Alzheimer's disease a highly sceptical field for pharmaceutical companies, researchers and investors. Although the huge clinical trials based on the two blockbuster candidates, bapineuzumab and solanezumab, failed to meet their primary efficacy endpoints, researchers believe that early therapeutic intervention could revive the beta-amyloid hypothesis. Despite the fact that controversies regarding the best approach to stop or delay Alzheimer's disease progression still persist, researchers believe that the current range of targets serve as a good reference point and need extensive clinical validation to gain approval. However, the significant advancement in scientific research for Alzheimer's diseases since 2003 ensures that things have been progressing in the right direction.