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The Ever Changing Landscape of Alzheimer's Drug Research

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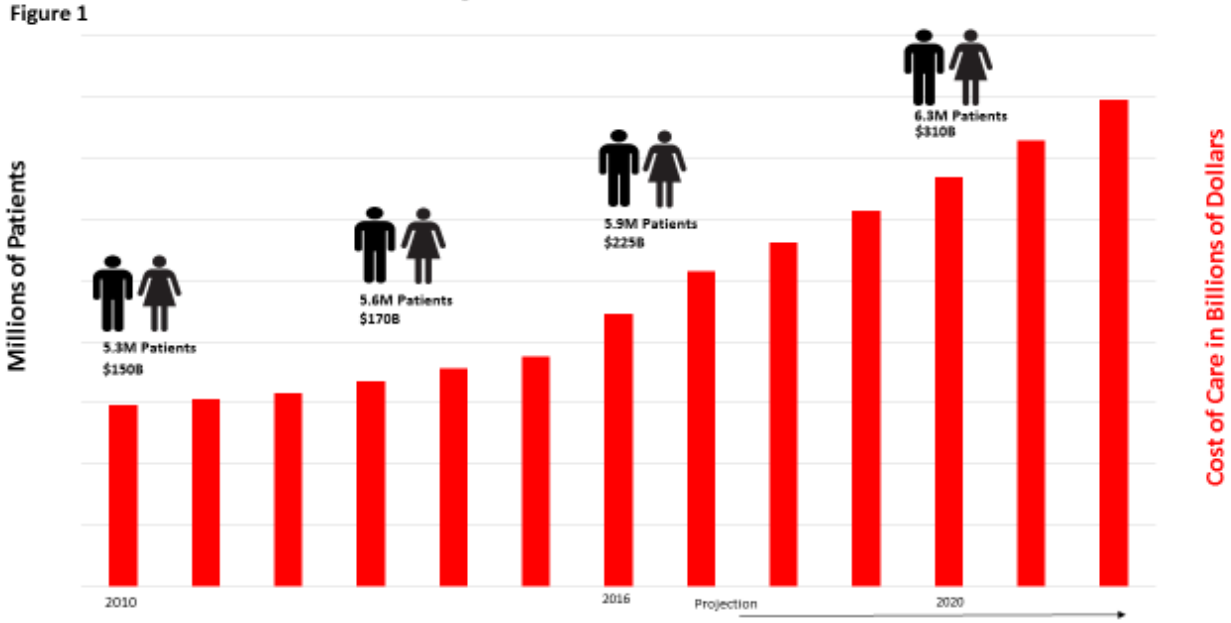
On a global basis, Alzheimer's affects over 9 million people and has an estimated annual cost of $600 billion for treatment, care and lost productivity. Furthermore, absent an effective treatment, the number of people diagnosed with Alzheimer's could triple by 2050. Given the number of people affected by the disease, both public and private research entities have dedicated a large amount of resources to finding a disease-modifying treatment or cure. However, one of the largest obstacles facing researchers is the question of what actually causes Alzheimer's. Specifically, is it the accumulation of amyloid plaque within the brain that causes the disease or is the plaque a neuro-protective response by the body? The purpose of this paper is to explore the amyloid plaque hypothesis as well as the various drugs in mid-to-late stage development.

The statistics that are associated with Alzheimer's are staggering. For instance, the mortality rate of a 70 year old patient diagnosed with Alzheimer's is significantly higher (50% over a ten-year basis) when compared to a person without the disease. Furthermore, the disease has an emotional and financial cost to a patient's family and friends. In 2016, it is estimated that 15.9 million family/friends provided 18.1 billion hours of unpaid care to Alzheimer's sufferers. From an economic perspective, the culmination of the above (including hospital costs) resulted in $225B in direct and indirect costs to the nation (Figure 1). These costs are expected to continue to grow, with 33% of all Medicare expenditures projected to be spent on Alzheimer's (and Dementia) by 2050, versus 20% or $117 billion in 2016.

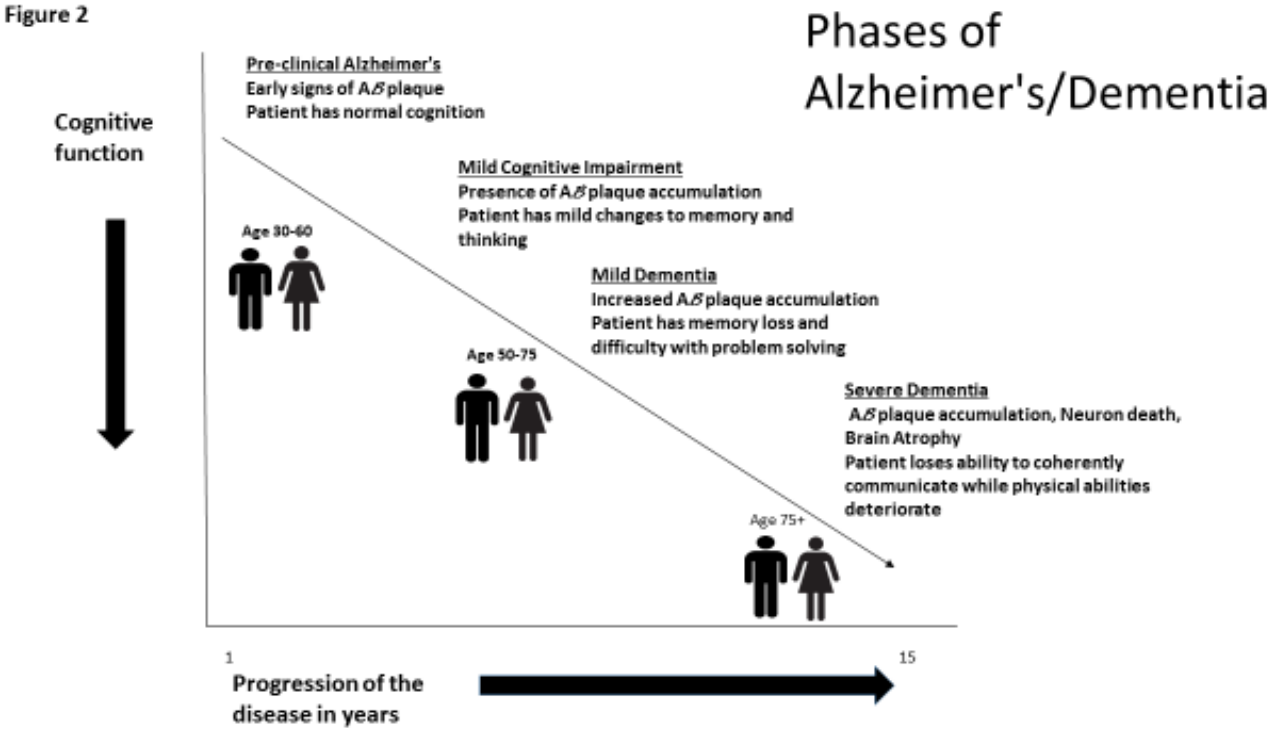
U.S. Patients Diagnosed with Alzheimer's versus Cost of Care

Figure 1



As noted in Figure 2, a patient usually develops Alzheimer's over a 10 to 15 year period, with the possibility of the negative effects evident at age 50, although the precursors to the disease could start much earlier in a person's life. Therefore, early diagnosis and intervention could be the key to preventing the loss of cognition.

Figure 2



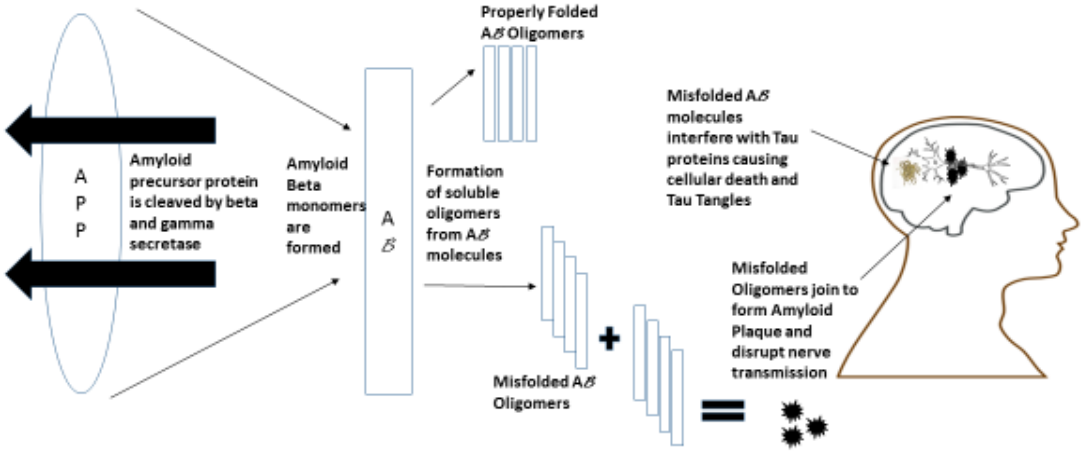
One issue researchers face is defining the cause of the disease. Although most research focuses on the accumulation of amyloid plaque within the brain and the ultimate destruction of neurons (causing brain atrophy), there are other potential causes including lifestyle (diet and smoking), prior infections and genetics (APOE-4 gene). Every person inherits a genetic copy of APOE from each parent, with the common forms being APOE-2, APOE-3 and APOE-4. It has been found that having a copy of the APOE-4 gene increases the risk of Alzheimer's by 20% to 25%, while women who inherit two copies have double the risk of contracting the disease (the incidence of the double gene has no effect in men). However, it should be noted that having APOE-4 does not mean a person will automatically contract Alzheimer's, as this could be correlation (similarity between patients) as opposed to causation.

The most prevalent hypothesis on the cause of Alzheimer's is the formation and accumulation of amyloid plaque within the brain. In its simplest form, the amyloid plaque-brain atrophy cascade is as follows:

1- Amyloid precursor proteins (APP) are cleaved (divided) by beta secretase yielding AB (amyloid beta).
2- AB molecules aggregate to form soluble oligomers (a molecular complex).
3- These oligomers can be misfolded and induce the AB molecule to also take the misfolded form.
4- The misfolded AB molecules aggregate (join) resulting in the formation of amyloid plaques that interfere/block nerve transmissions.
5- The amyloid plaque may also trigger an inflammation response by the body which disposes of the disabled brain cells, eventually causing brain atrophy.

Tau proteins, which are abundant in central nervous system neurons, can also be influenced by the misfolded oligomers. Specifically, the microtubule structure inside the cells collapses as it is unable to receive nutrients, resulting in a twisted strand of dead cells within the neuron called a tangle. Taken together, both amyloid plaque and tau tangles interfere with cell signal transmission, causing cell death, loss of cognition and eventual brain atrophy (Figure 3)

Figure 3 **Simplistic Model of the Formation of Amyloid Plaque and Tau Tangles**

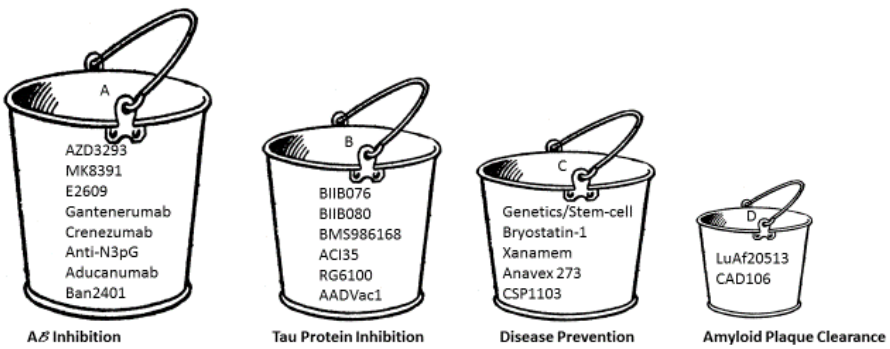


Although there have been many attempts to find an effective treatment, the Alzheimer's discovery field has experienced a large number of drug failures (100+). One of the more recent high profile failures was Solanezumab from Eli Lilly. In the last stage of clinical testing (phase three), the drug showed a small but statistically insignificant improvement in cognition. The failure occurred despite a well-designed clinical trial that limited the patient population to people with amyloid plaque, with the drug administered to patients before they reached the severe stage of the disease (hoping to halt the progression of the disease before damage occurred). One other high profile setback highlights another issue facing researchers: safety. Although Biogen's drug, Aducanumab, remains in clinical development, in mid-stage testing the drug increased cerebral edema (swelling) in patients carrying the APOE-4 gene, a major issue since a large portion of Alzheimer's patients have this gene. Biogen has re-designed the trial and is now titrating (slowly raising) the dose of the drug which could alleviate the edema issue.

Although these high profile failures were a major blow to the beta amyloid plaque hypothesis, most mid-to-late stage clinical programs still use this hypothesis as a basis. With this in mind, most of the drugs in development revolve around one of three targets: the inhibition of secretase, inhibition/removal of amyloid beta and the inhibition/removal of tau. For simplicity purposes, the different Alzheimer's therapeutic targets have been divided into four buckets (Figure 4). It should be noted that each therapeutic bucket does not include a comprehensive list of all drugs in development, only a cross representation of drugs in the non-preclinical stage.

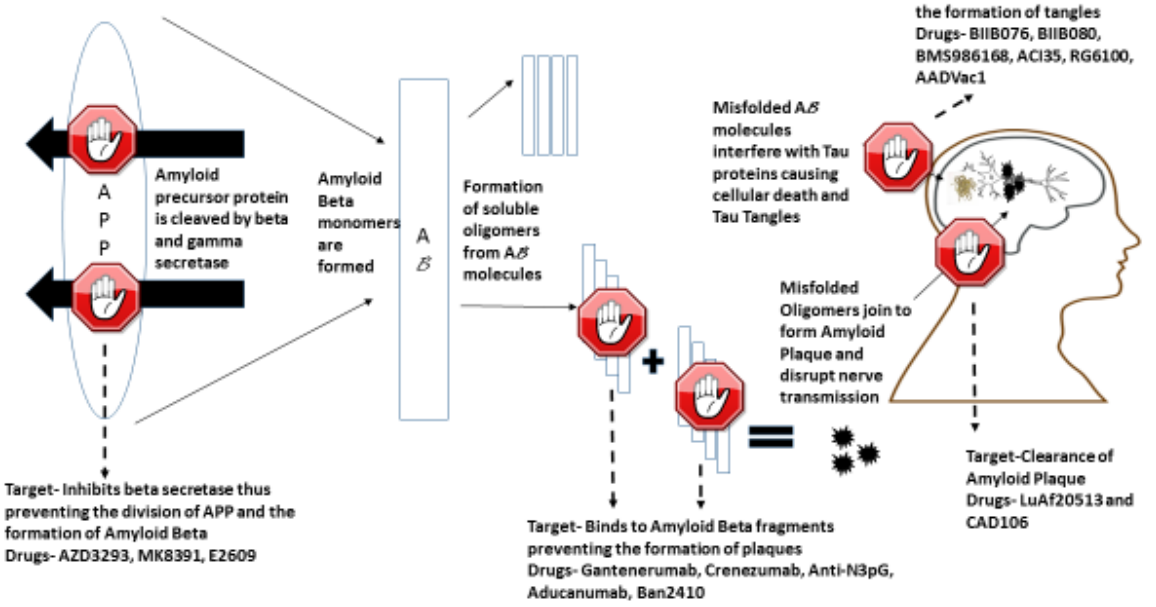
Figure 4

Alzheimer's Therapeutic Buckets



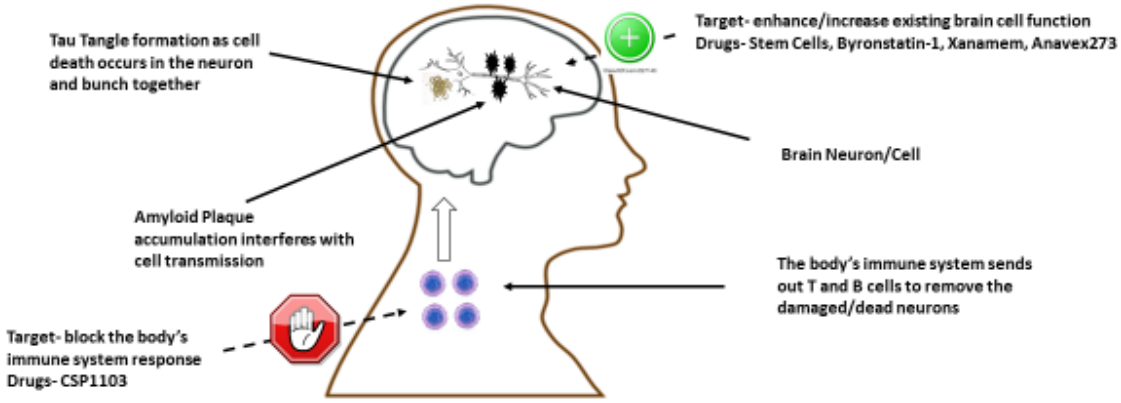
Each bucket of drugs attacks Alzheimer's at different stages of the disease and utilizes alternative pathways to try and block its degenerative effects. Using the simplistic model of the Formation of Amyloid plaque and Tau Tangles introduced earlier in the paper, Figure 5 illustrates how each drug interacts with the different pathways to either try and stop the progression of the disease (stabilization) or clear the existing plaque/tangles.

Figure 5 Simplistic Model of the Formation of Amyloid Plaque and Tau Tangles



Unlike the other therapeutic buckets, the disease prevention drugs (bucket C) are additive, with the goal of enhancing brain cognition by boosting neuron/brain cell transmission, adding back lost cells (stem cell implantation) and limiting the loss of damaged brain cells (inhibiting an immune response). Furthermore, highlighting the significance of these therapies is the fact that, for the most part, brain cells do not replicate once they are lost, so the need to preserve and boost the surviving cells is important to cognition. In theory, this should directly relate to a boost in memory, problem solving and physical ability (Figure 6).

Figure 6 Simplistic Model of the Brain, Neurons and the Negative Effect of Alzheimer's



The effects of Alzheimer's are devastating for the patient, their family and their friends. Furthermore, the associated costs of the disease continue to escalate and will surpass the estimated $600 billion spent in 2016. Despite the number of high profile drug failures, researchers have not been deterred, as the number of drugs in clinical trials continues to increase with the amyloid plaque hypothesis as their main drug discovery basis. Furthermore, with each drug failure researchers learn more about the disease, including the possible need to treat the disease with multiple drugs and at different stages of a patient's life. One potential key to drug discovery is diagnostics: identifying which patients would benefit most from the various therapies, and at what age the drug should be administered. In any case, Alzheimer's has reached an epidemic status. Without an effective treatment, the disease will continue to have an emotional and economic impact for generations to come.

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