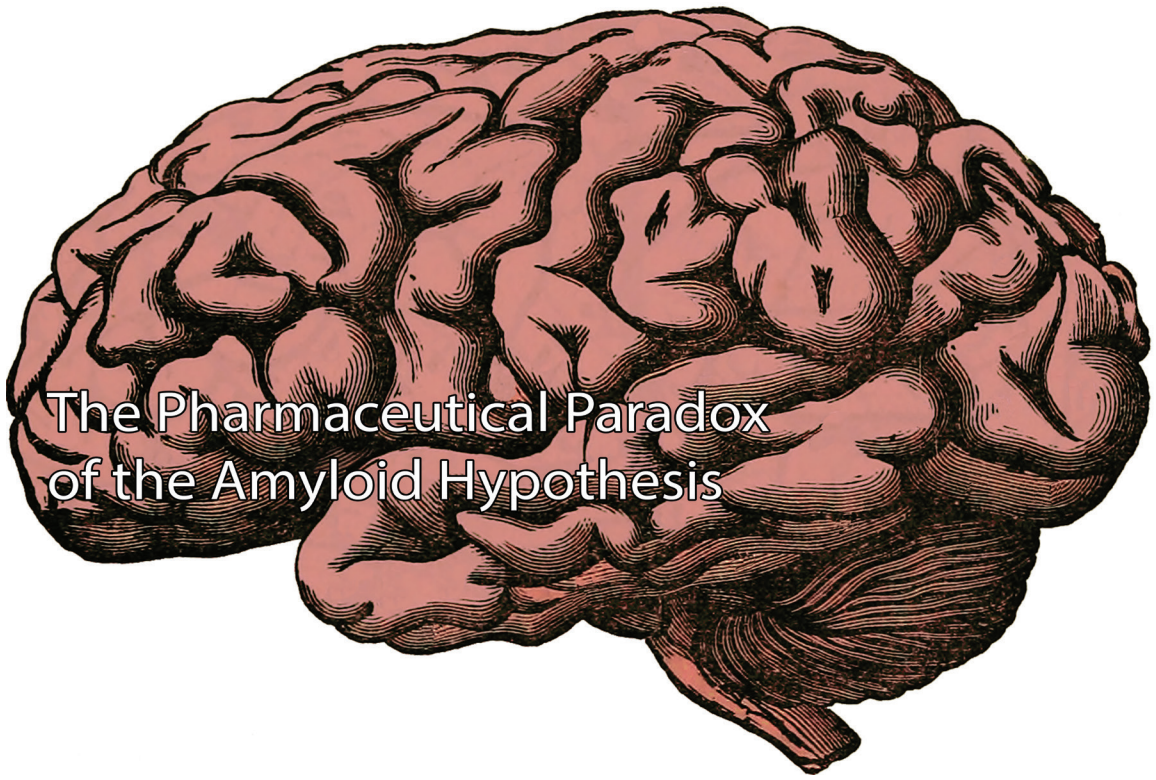

The Pharmaceutical Paradox of the Amyloid Hypothesis

Brandon Gong '22

This past October marked the biggest pharmaceutical surprise of 2019. Biogen, after discontinuing Phase III clinical testing for its flagship anti-Alzheimer's drug candidate, aducanumab, has now submitted the same therapeutic for FDA approval based on results from a larger clinical dataset. This announcement was a huge reversal of fortune for the Cambridge-based pharmaceutical company, which saw its stock prices soar after experiencing a disappointing downfall earlier in the year, when it originally pronounced aducanumab as a failure.

"AD drug development has been littered with over a hundred pharmaceutical failures"

For the scientific community at large, this news represents a key milestone in the search for the first disease-modifying cure for Alzheimer's disease (AD). However, even in light of this exciting turn of events, it is important to remember that there is still much to be uncovered in the fight against AD. The twenty-year history of AD drug development has been littered with over a hundred pharmaceutical failures and no effective treatment for stopping the disease. Biogen's spring discontinuation of aducanumab had caused many researchers to step back and re-evaluate the direction of the AD field. Specifically, the validity of the foundational theory of AD research, the amyloid hypothesis, had been facing more scrutiny than ever before, and AD scientists were beginning to take new directions in their research. Now, aducanumab's resurrection leaves researchers at a crossroads regarding the long-standing amyloid hypothesis.

Background of AD and the amyloid hypothesis

AD is an irreversible, chronic progressive neurodegenerative disorder that destroys memory, learning, and other important mental functions. The public health issue that AD presents cannot be overstated. One in three will develop AD or another similar form of dementia over the course of their lifetimes. Furthermore, among the top ten leading causes of death in the United States, AD is the only one that cannot be prevented, cured, or slowed down (2016 Alzheimer's Disease Facts and Figures Report).

To date, the FDA has only approved of four unique medications for AD. However, these drugs merely aid in temporary symptomatic relief of AD, and do not affect the underlying disease pathology or prevent disease

progression (Mielke). As a result, an estimated 5.4 million Americans live with AD, costing the nation an estimated $236 billion in healthcare costs. Due to the lack of effective disease-modifying therapeutics on the market, this population is only expected to continue to rise; by 2050, it is estimated that 14 million Americans will be afflicted with AD (2016 Alzheimer's Disease Facts and Figures Report).

"An estimated 5.4 million Americans live with AD"

For nearly thirty years, the central basis behind most AD research has been the amyloid hypothesis. This theory postulates that the accumulation of amyloid-beta (Aβ) protein deposits in the brain leads to the development of tau protein tangles, ultimately resulting in neuronal death, synaptic loss, and eventually, dementia (Selkoe and Hardy). This proposed mechanism is often referred to as the "amyloid cascade", as it is the formation of toxic Aβ deposits that triggers the overall disease pathology. These Aβ deposits are formed from the excessive aggregation of Aβ proteins, which are cleaved from amyloid precursor protein (APP) by two enzymes: β-secretase 1 (BACE1) and γ-secretase (O'Brien and Wong).

The prevalence of Aβ protein in the post-mortem brains of AD patients, along with ample evidence of Aβ neurotoxicity in cell and animal models, led researchers to support this theory. For example, mice that are genetically altered to overexpress Aβ develop rapid memory loss that is strongly reminiscent of AD symptoms in humans (Sasaguri). Moreover, mutations in genes that code for APP and presenilin 1, the active region of γ-secretase, have been critically linked to increased risk of developing early-onset AD (Tanzi and Bertram). Further clinical evidence stems from humans with Down's syndrome, who retain three copies of chromosome 21 – the chromosome that harbors the *APP* gene – and tend to experience the neuropathological symptoms of AD at higher rates than humans without this chromosomal abnormality (Wiseman). Summarily, due to the observed correlation between Aβ and AD, AD drug development has largely centered around the inhibition of Aβ production or the clearance of Aβ plaques from the brain.

Therapeutic development for AD

Yet, for all of the basic research findings that implicate amyloid in the progression of AD, there has been no success in translating these results into a cure – until recently. Dozens of amyloid-based therapeutics, ranging from BACE1 and γ-secretase inhibitors to reagents that are designed to specifically bind Aβ, have all failed in clinical drug trials, with varying reasons as to why. In the past, -secretase inhibitors were shown to interfere with critical cellular signaling pathways, resulting in debilitating side effects to patients (Xia). BACE1 inhibitors have been associated with steeper cognitive decline in treated subjects when compared to the control, untreated AD patients (Selkoe). Previous Aβ antibodies had also failed to retain positive results in clinical testing. Both crenezumab and solanezumab, which are monoclonal antibodies that target specific forms of Aβ peptides, were unable to ameliorate memory and mitigate cognitive decline in patients when compared to placebo (van Dyck). These failures, including aducanumab's previous discontinuation, led many researchers to question the role of amyloid in AD; some scientists have argued that amyloid is merely a byproduct of larger mechanistic damage in the brain, and therefore not a viable option to target for the alteration of disease progression.

Aducanumab's recent drug trial success now presents a refutation to detractors of the amyloid hypothesis. Although aducanumab is also a monoclonal Aβ antibody, there are several aspects that differentiate aducanumab

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from its failed predecessors. Aducanumab was developed through a process called "reverse translational medicine", in which operative antibodies from the immune systems of healthy, aged donors who had successfully resisted AD are screened for reactivity with Aβ (Sevigny). As such, aducanumab is able to bind Aβ aggregates, including forms of the protein are thought to be more toxic than previously targeted variants. Based on promising preclinical results, Biogen launched two Phase III clinical trials, EMERGE and ENGAGE, in late 2015.

In March 2019, a futility analysis rendered a negative result for aducanumab, predicting that these studies were unlikely to meet their primary endpoints upon completion. As a result, Biogen discontinued further testing for aducanumab, which was devastating blow for the AD community at large. However, this futility analysis was only based on data up until December 2018. After the discontinuation of these studies, additional data from

the trials – now up until March 2019 - became available. An analysis of this larger dataset revealed that in the EMERGE trial, treatment with the high-dose variant of aducanumab was able to significantly reduce cognitive decline when compared to placebo. This finding, along with preliminary meetings with the FDA, led Biogen to reverse its decision on aducanumab in October 2019.

Whether the FDA finds these new results compelling enough to approve aducanumab remains up in the air. It's important to note that data from EMERGE demonstrated that aducanumab significantly decreased cognitive decline compared to placebo; the results from ENGAGE did not support these findings outright. Nevertheless, the consequences of Biogen's resurrection of aducanumab remain something to look out for in the coming years. For decades, the amyloid hypothesis had reigned as the dominant theory of AD pathogenesis. Yet, in this time, no tangible therapeutic progress was realized, all while the population of AD patients increased exponentially. The cancellation of aducanumab back in March 2019 had heralded much change in how scientists are planning to approach future AD research. In the summer of 2019, AD research conferences stressed diversification in the field, with a special emphasis on the development of diagnostic AD biomarker tests. Even though aducanumab appears to have breathed new life into amyloid hypothesis, this news should not detract from the scientific pursuit of other methods for AD treatment. The AD community cannot risk keeping all of its eggs in the amyloid basket for any longer.

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