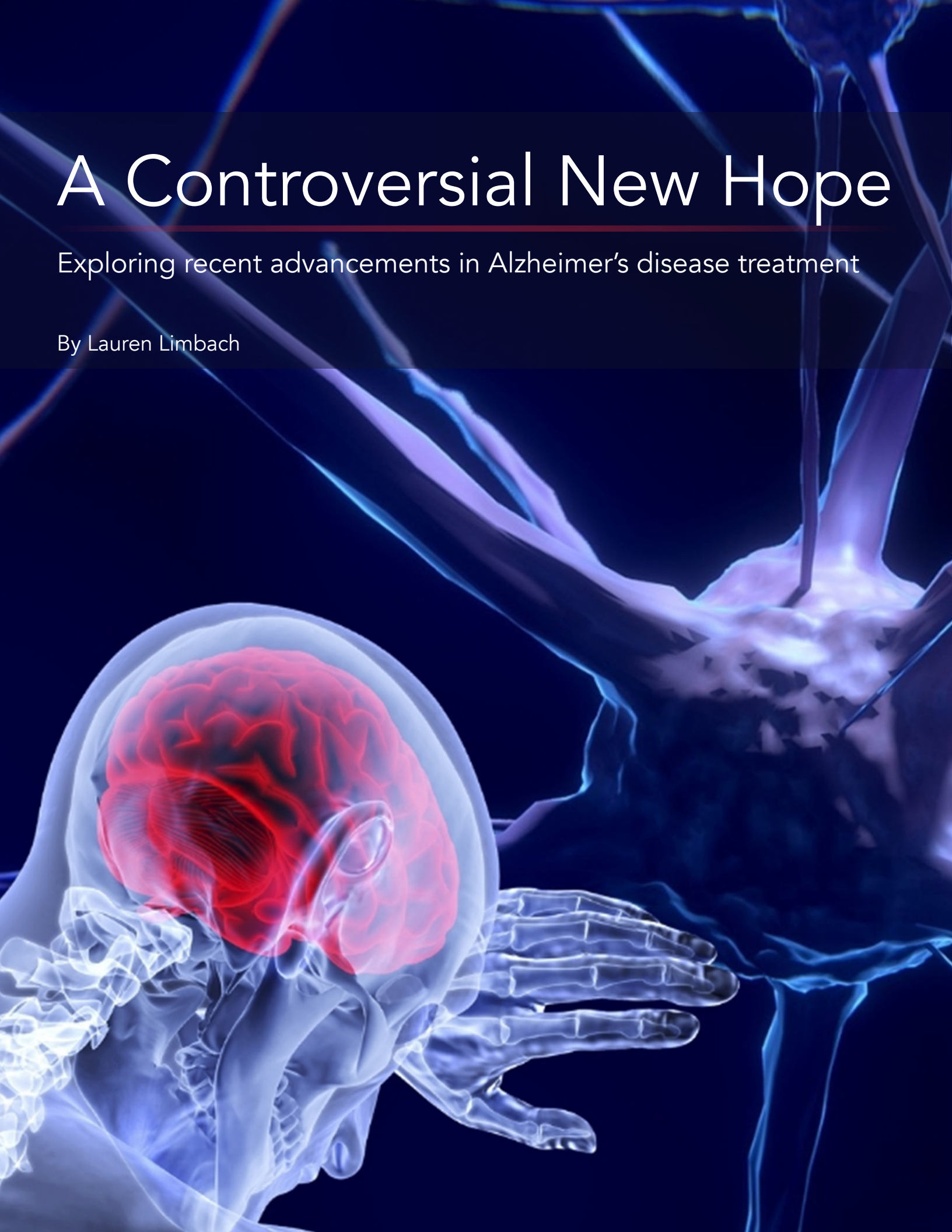
A Controversial New Hope

Exploring recent advancements in Alzheimer's disease treatment

By Lauren Limbach



The Aduhelm Controversy

Most people would probably acknowledge that they've made a mistake at work from time to time. This is what happened to *Joe, a successful industrial researcher, who one day noticed that he had made a calculation error while at work. But this wasn't an isolated incident, these types of calculation errors kept happening with increasing frequency. Eventually the repeated mistakes forced him to step away from a job in which he used to thrive. This trend continued for several years, causing him to bounce from job to job, before he was eventually fired and became unemployed. But the changes that Joe experienced weren't limited to mistakes at work. Joe began having difficulty navigating places he had been many times before, and eventually he lost the ability to perform many basic tasks such as maintaining personal hygiene [1]. Based on these symptoms, you may not be surprised to learn that Joe was eventually diagnosed with Alzheimer's disease (AD). However what may be surprising is Joe's age: he was diagnosed with AD at the age of 37 [1].

Alzheimer's disease (AD) is a neurodegenerative disease characterized by drastic deteriorations in a patient's cognition, memory and overall function — all of which were observed in Joe's case [2]. AD also imposes large financial and emotional burdens on families and caregivers, and often necessitates entry into a nursing home [3]. The vast majority of AD diagnoses are made in elderly individuals, while a smaller number of cases like Joe's are diagnosed early in life [2]. Over 6 million Americans are currently living with AD, yet AD is not often a topic of daily conversation despite the widespread and devastating effects imposed by the disease [3].

However, in the summer of 2021, AD was frequently featured in media headlines because of the US Food and Drug Association's (FDA) decision to approve Aduhelm: an innovative new drug designed to treat AD. Despite being the first AD drug approved in twenty years, the media coverage of Aduhelm's approval was largely negative. Confusion over the drug's efficacy and the basis for the FDA's decision overshadowed what could have been a victory for everyone involved in the fight against AD. Shortly following the approval of Aduhelm, stories detailing the departure of several members of the FDA's advisory board began circulating in the news. These individuals cited their disagreement with Aduhelm's approval as the motivating factor behind their departure from the FDA, stirring public intrigue as to whether or not the FDA's decision was a sound one [4]. After the board members' departure, the acting FDA commissioner initiated an external investigation into the proceedings that led to Aduhelm's approval [5]. The acting commissioner stated that the primary motivation for launching the investigation was to reestablish public confidence in the FDA approval process [5]. However, launching the external investigation fueled the fire of public speculation that something was amiss in regards to Aduhelm's approval. What followed over the next several weeks was an onslaught of attention-grabbing headlines such as:

"How Aduhelm, an unproven Alzheimer's drug, got approved"
- New York Times

"FDA Approved Biogen Alzheimer's Drug Despite Some Staff Concerns"
- Wall Street Journal

"New Alzheimer's drug could cost the government as much as it spends on NASA"
- New York Times

Overall, the media coverage of Aduhelm painted the drug as an uninspiring advancement in AD treatment, and a potential misstep by the FDA. Many articles questioned the efficacy of Aduhelm [6], [7], and others highlighted the high price tag associated with the drug [8], [9]. Some characterized the rollout of the drug as unsuccessful and cited numerous reputable hospitals and insurance companies who were choosing not to prescribe or cover Aduhelm [10], [11].

Additionally, in October of 2021 the biotechnology company Eli Lilly filed for FDA approval of their new Alzheimer's drug, Donanemab, which is mechanistically quite similar to the controversial Aduhelm drug [12], [13], [14]. This raises the question of whether or not the FDA will grant approval to an AD drug similar to Aduhelm after the backlash that resulted from their original approval. The Aduhelm controversy and recent developments with Donanemab highlight the importance of investigating the biological basis of AD, as well as how these treatments fit into our current understanding of AD.

Are amyloid-β proteins the underlying cause of AD?

For the last several decades, the most commonly accepted explanation for AD has been the amyloid-β hypothesis: AD symptoms arise due to aggregations of amyloid-β proteins in the brain [15]. According to the biological definition of AD, the buildup of amyloid-β proteins is a necessary precursor for an individual to be diagnosed with AD [16]. Amyloid-β proteins are derived from the breakdown of the amyloid precursor protein (APP): a protein that is found in neurons and that plays an unknown role in their growth and survival [17]. APP is normally broken down by an enzyme called the α-secretase (Figure 1), [17]. The breakdown of APP by α-secretase produces benign byproducts that do not contribute to AD pathology [17]. However APP can also be broken down by two different enzymes, β-secretase and γ-secretase, which yield slightly different products than those produced by the normal pathway (Figure 1), [2]. Among those products are amyloid-β proteins [2]. The physical properties of these amyloid-β proteins make it easy for them to combine into clumps, referred to as insoluble plaques or fibrils [17]. Amyloid-β plaques are arguably the most prominent feature of AD pathology, and are thought to underlie the cognitive and behavioral abnormalities associated with AD [2]. Research has suggested that the balance between the two pathways for breaking down APP is different in AD patients compared to non-AD patients, leading to increased production of amyloid-β in AD patients [2].

If there is so much evidence that amyloid-β is the underlying cause of AD, then why have the collective efforts of researchers around the globe not resulted in an amyloid-β-clearing treatment capable of curing AD? And why are there studies circulating saying that the severity of amyloid-β plaque buildup isn't even predictive of the severity of AD symptoms [2]? There are several viable theories for why this is the case. Some scientists think that the initial presence of amyloid-β proteins, rather than the quantitative buildup of amyloid-β over time, triggers a chain of events that leads to the clinical symptoms of AD [2]. In this scenario the quantitative extent of amyloid-β buildup would not predict symptom severity because the symptoms would not result from amyloid-β aggrega-

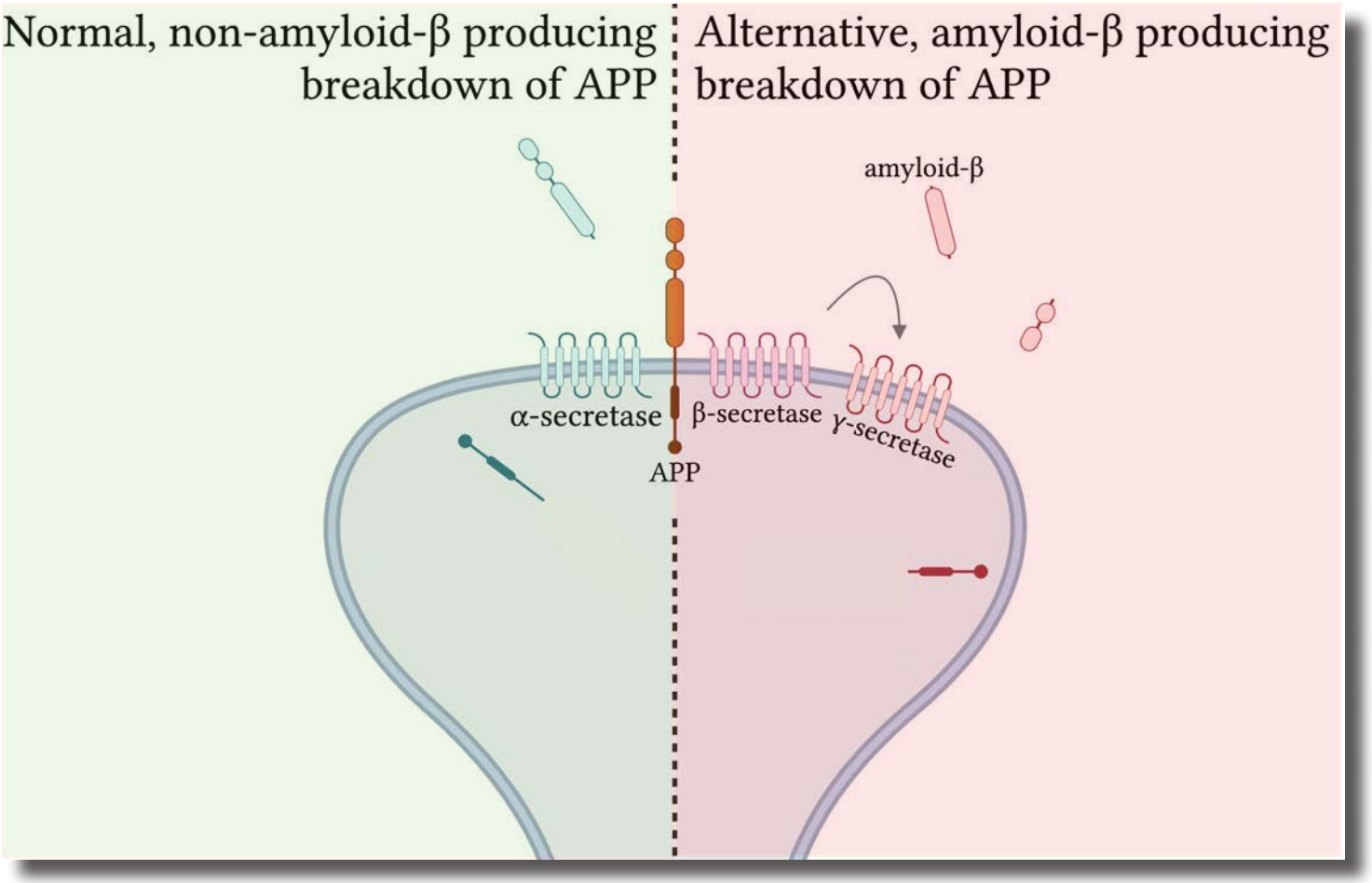


Figure 1. Possible pathways for APP breakdown. Original image by Lauren Limbach. Created in BioRender.

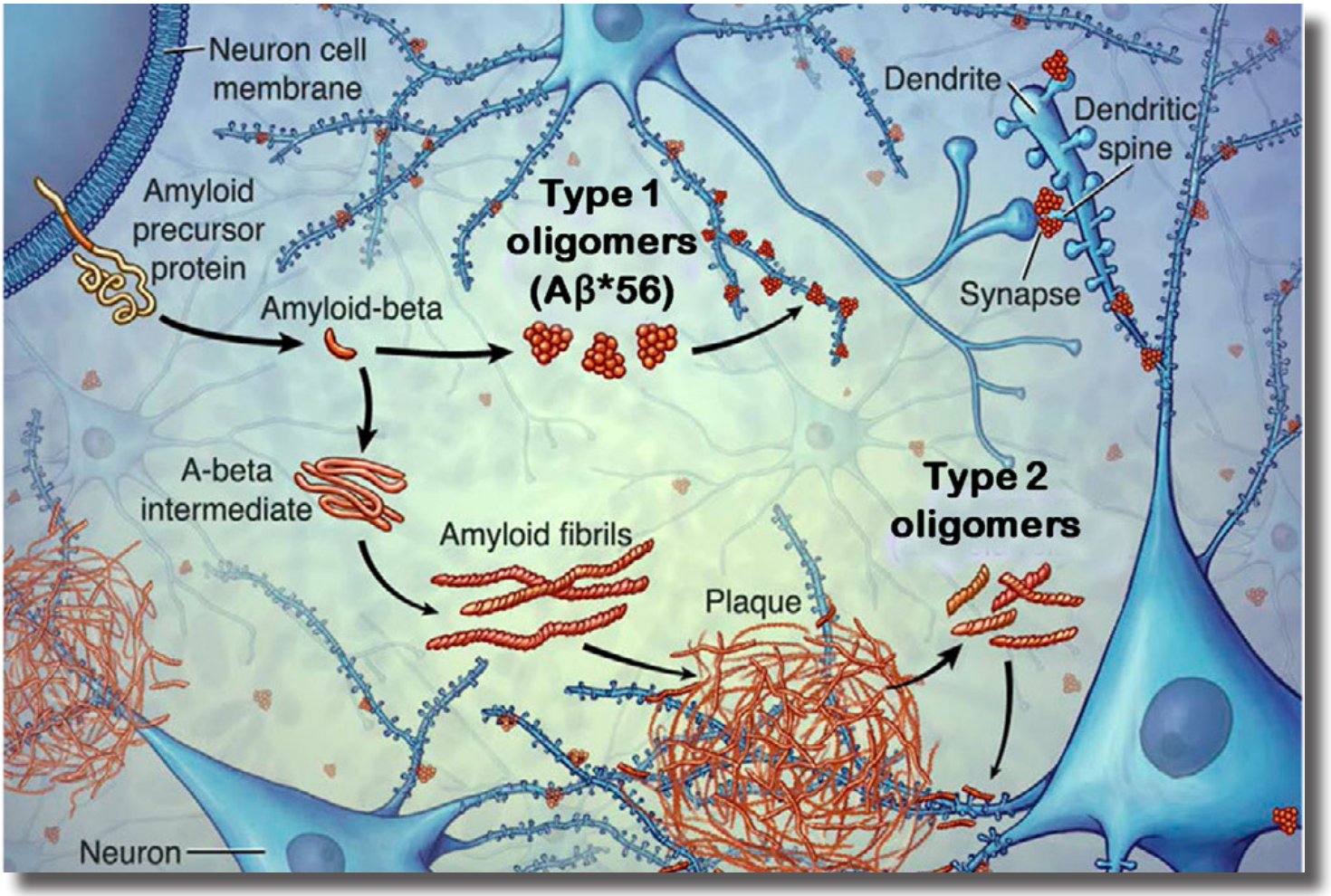


Figure 2. "Biogenesis of types 1 and 2 Aβ oligomers in the brain" by Karen Hsiao Ashe is available under CC BY-NC 4.0. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7984270/)

tion, but would instead result from meree amyloid-β presence [2]. Should this theory be true, amyloid-β-clearing drugs would likely prove ineffective in alleviating the symptoms of AD once the initial presence of amyloid-β triggered the ensuing downstream effects [2]. A second theory suggests that only a subset of amyloid-β proteins are AD-causing agents, and that the clinical symptoms of AD are associated with the quantity of these particular amyloid-β subtypes, as opposed to amyloid-β aggregation as a whole [2]. If this is the case, amyloid-β-based treatments for AD would only be effective if they target the specific disease-causing subtypes of amyloid-β [2].

In fact, recent developments in AD research support the hypothesis that not all amyloid-β buildup plays an equal role in AD pathology. Most AD pharmaceutical trials target insoluble amyloid-β: clusters of amyloid-β oligomers that form a plaque or fiber [18]. However another form of amyloid-β, soluble amyloid-β oligomers, may be wreaking the most havoc in the brains of AD patients [18], (Figure 2). Soluble amyloid-β oligomers are smaller and more mobile than amyloid-β plaques, and appear to be more toxic than insoluble amyloid-β oligomers [2]. If this is the case, the many unsuccessful attempts to treat AD by dissolving amyloid-β plaques may be due to the fact that the soluble amyloid-β oligomers, rather than the insoluble plaques, are to blame for AD symptoms [18].

So what do scientists think are the effects of soluble oligomers and how do they lead to the devastating clinical symptoms of AD? They are perhaps implicated in the ability to form memories. Memory formation is a complex process, and its loss is perhaps the most commonly recognized symptom of AD. Memory formation relies on a complex molecular process called long-term potentiation in which the connections between certain neurons in the brain are strengthened over time [19]. Soluble amyloid-β oligomers are capable of altering the proteins on the exterior of neurons, which can prevent long-term potentiation from taking place (Figure 3), [19]. The hindrance of long-term potentiation in AD patients by soluble amyloid-β oligomers would provide a powerful explanation for the memory loss and cognitive deficits experienced by AD patients. Furthermore, overall cognitive functioning is dependent

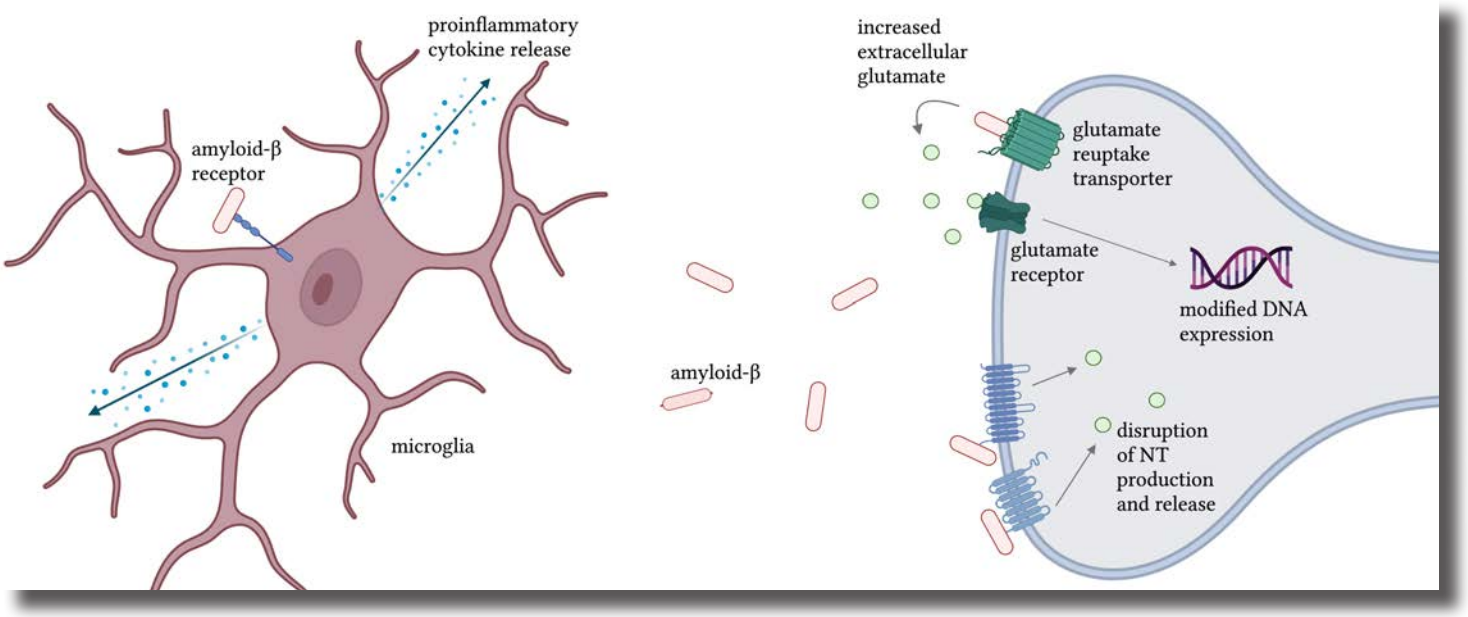


Figure 3. Downstream effects of amyloid-β proteins. Original image by Lauren Limbach. Created in BioRender.

on timely and accurate communication between neurons. This occurs via the release of small biological containers called synaptic vesicles that contain messenger molecules called neurotransmitters [19]. Soluble amyloid-β oligomers have been demonstrated to interact with many of the proteins involved in synaptic vesicle generation and release, providing a potential pathway through which amyloid-β oligomers may interfere with neuronal communication and as a result, cognitive functioning (Figure 3), [19].

Neuroinflammation in AD

Recently there has been an increased focus on the link between amyloid-β aggregation and neuroinflammation, as well as what role this relationship plays in AD pathology. Neuroinflammation occurs when the brain's immune system is activated in response to a threatening stimulus such as a foreign pathogen [17]. Neuroinflammation is mediated by microglia: a group of cells within the central nervous system (CNS) that are responsible for defending the brain and spinal cord from exterior threats [17]. Microglia are essential for maintaining stability within the CNS, and as such, microglial and neural immune dysfunction have been speculated to play a role in AD [17].

Microglia are responsible for clearing amyloid-β following its secretion from neurons [17]. It is important for amyloid-β to be broken down soon after its release because its molecular makeup makes it easy for it to assemble into oligomers and plaques [17]. The delicate balance of amyloid-β secretion and removal can be upset and result in amyloid-β accumulation if neurons increase their production of amyloid-β to the point where the microglia can't keep up [17].

When microglia detect a threat in the environment, they enter a distinct activated state and release molecules called proinflammatory cytokines that promote inflammation and other immune responses [17]. Microglia contain receptors capable of identifying amyloid-β in their environment, meaning that microglia become chronically activated following amyloid-β accumulation [17]. This chronic activation causes microglia to release copious amounts of the proinflammatory cytokines TNF-α and Il-1β, which have been found in higher levels in the brains of AD patients [17]. While microglial activation and proinflammatory cytokine release may be helpful following exposure to an isolated pathogen, the long-term continuation of these responses is damaging to the brain [17]. Elevated TNF-α and Il-1β levels have been associated with declining cognitive abilities, suggesting a direct role for neuroinflammation in a hallmark characteristic of AD clinical pathology [17]. Neuroinflammation may also increase the severity of AD pathology in patients because there is a positive feedback loop between neuroinflammation and amyloid-β production: neuroinflammation activates the enzymes that generate amyloid-β, increasing its accumulation in the brain over time [17]. However, the precise role that neuroinflammation plays in AD pathology remains unclear, making it a promising area of future research — particularly as the search continues for effective treatments for AD.

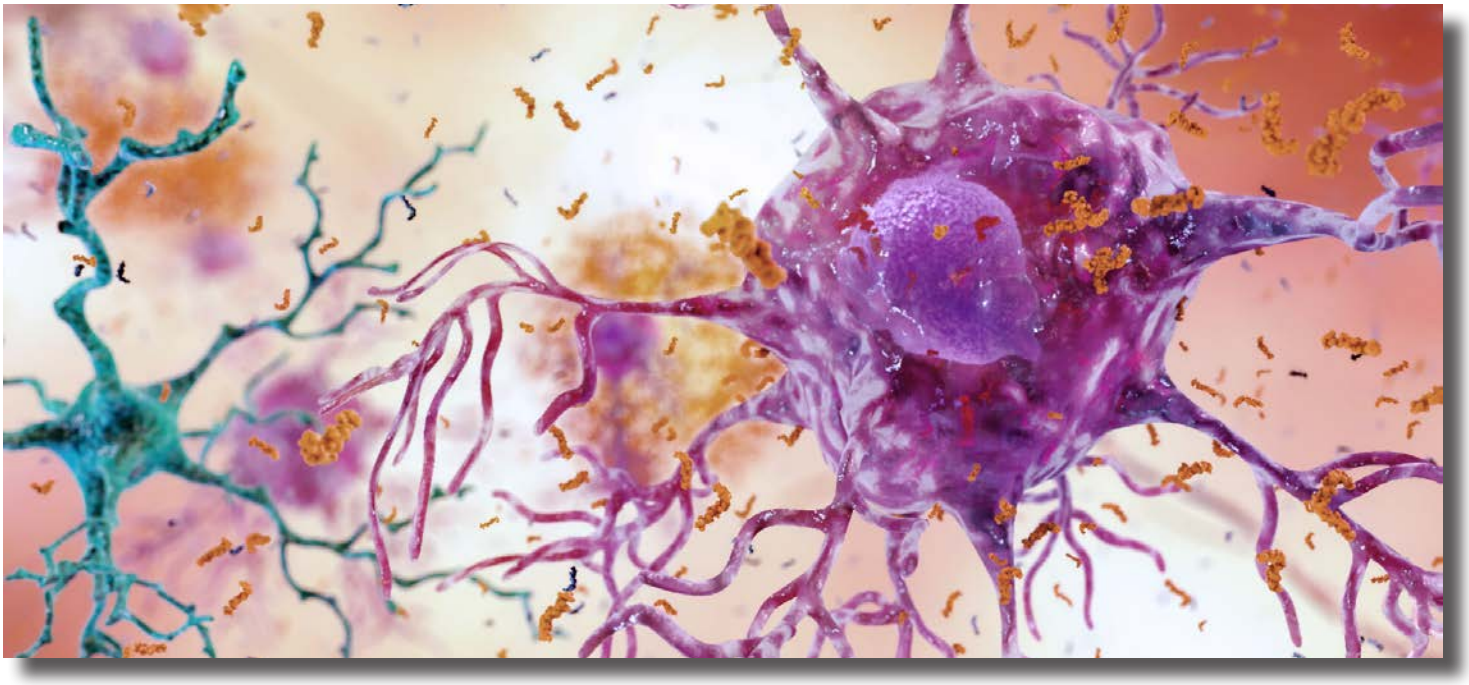
Current treatments for AD

The Alzheimer's Association website breaks down the currently available pharmaceutical treatments for AD into two broad categories: "Drugs that may change disease progression" and "Drugs that treat symptoms" [20]. Aduhelm is the only drug that is acknowledged to potentially possess the ability to change disease progression of AD. The other drugs may be effective at addressing the symptoms of AD, but have no effect on the eventual advancement of the disease. These symptom-oriented drugs fall into four classes: cholinesterase inhibitors, glutamate regulators, cholinesterase inhibitor + glutamate regulator combinations and orexin receptor antagonists [20]. The drugs in each category mitigate AD symptoms by targeting neurotransmitter systems that are disrupted in the brains of AD patients. Therefore, these drugs attempt to remedy the downstream effects of amyloid-β aggregation, rather than directly addressing amyloid-β aggregation itself.

Cholinesterase inhibitors, one class of symptom-oriented AD drugs, prevent the breakdown of the neurotransmitter acetylcholine [21]. The acetylcholinergic system is integral to memory formation, and AD-associated memory loss likely partially results from decreased acetylcholine production due amyloid-β aggregation [22]. Furthermore, decreased acetylcholine activity may increase the formation of amyloid-β plaques [22]. Cholinesterase inhibitors that increase acetylcholine activity therefore not only address the shortage of acetylcholine that results from amyloid-β formation, but may slow the pace of amyloid-β accumulation by elevating acetylcholine activity. Clinical trials have demonstrated that cholinesterase inhibitors are capable of improving the cognitive abilities and overall functioning levels of AD patients, albeit to a limited extent [22], [21].

In addition to the acetylcholine system, another neurotransmitter system associated with AD pathology is the glutamate system. Amyloid-β affects glutamate activity in an opposite manner than it does acetylcholine. By blocking the reuptake of glutamate molecules back into neurons, amyloid-β aggregation leads to an excess of glutamate that continually activates neuronal glutamate receptors (Figure 3) [19]. Overactivation of glutamate receptors can lead to changes in gene expression that impact cell functioning and survival [19]. Glutamate regulating drugs designed to treat AD block neuronal glutamate receptors, thus preventing the buildup of glutamate from overactivating glutamate receptors [23]. Similar to cholinesterase inhibitors, glutamate regulators are capable of improving cognitive and global functioning levels to a limited extent in AD patients [23]. Glutamate regulators are often prescribed in addition to cholinesterase inhibitors [23]. Simultaneous treatment with both classes of drugs may improve outcomes by addressing the separate effects of amyloid-β aggregation on two different neurotransmitter systems.

The other drug category listed on the Alzheimer's Association website consists of orexin antagonists. Orexin is a neurotransmitter responsible for keeping individuals awake and alert [24]. Its role in AD is support-



"Brain Inflammation from Alzheimer's Disease" by NIH Image Gallery. 2017. Flickr.

ed by the fact that patients with moderate to severe AD exhibit increased orexin levels compared to patients with mild AD [24]. Furthermore, AD patients often exhibit abnormal sleep/wake cycles, including insomnia: the primary AD symptom that orexin antagonists are designed to treat [24]. Orexin dysregulation and amyloid-β aggregation also appear to be connected. Blocking orexin activity reduces amyloid-β levels, suggesting that orexin influences amyloid-β dynamics, although the precise nature of this relationship remains unknown [24].

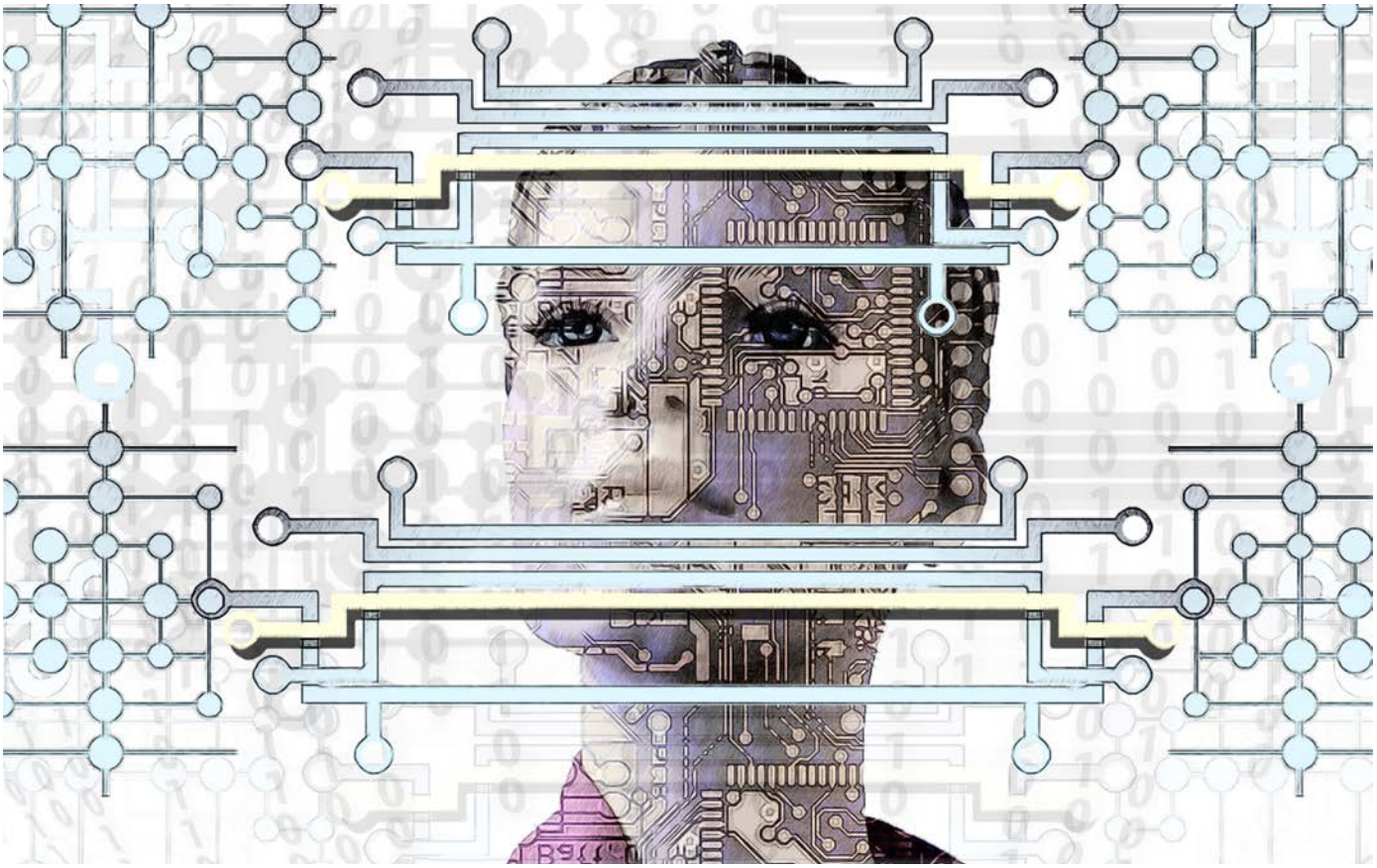
The current treatment options available to AD patients attempt to address the symptoms of AD through a variety of pharmaceutical methods targeting different neurotransmitter networks. While these treatments may have positive impacts on the patient's cognitive and functional abilities, or delay the patient's entry into a nursing home, they do not address the underlying causes of AD, and therefore do not represent a cure. The only drug that currently targets the underlying biology of AD is Aduhelm. However, even the Alzheimer's Association website states that Aduhelm "may change disease progression," indicating that a lot of uncertainty remains regarding its efficacy. So how exactly does Aduhelm work? And in what ways is it different from the current treatments available to AD patients?

Aduhelm and Donanemab

Instead of addressing the adverse effects of amyloid-β aggregation, Aduhelm and Donanemab target amyloid-β aggregation itself. Both Aduhelm and Donanemab belong to a class of pharmaceuticals known as monoclonal antibodies [12], [14]. Antibodies are generated naturally by our immune system and are used to identify and destroy potentially harmful pathogens [25]. In recent decades, antibody production has been harnessed by the biotechnology industry to produce therapeutic monoclonal antibodies. Biotechnology companies can design and produce antibodies that target biological threats of interest. The antibodies are then administered to patients to prompt the immune system to mount an attack against the pathogen of interest. In addition to their use in AD treatments, monoclonal antibodies can be used to treat a host of other disorders from asthma to leukemia, and have recently demonstrated potential for treating COVID-19 [25], [26]. Currently therapeutic antibody treatments are one of the largest areas of biomedical research and account for 50% of biomedical sales revenue [27].

Aduhelm and Donanemab both attempt to treat the underlying biological cause of AD by using monoclonal antibodies to target and breakdown amyloid-β plaques in AD patients [12], [14]. The main difference between the two drugs is that Aduhelm targets the entire amyloid-β sequence in humans, while Donanemab recognizes a specific region of the amyloid-β protein [12], [14]. Because of their slightly different targets, Aduhelm and Donanemab have differing abilities to bind soluble and insoluble amyloid-β. Aduhelm is capable of binding soluble amyloid-β oligomers and insoluble amyloid-β plaques, whereas Donanemab's more targeted sequence means that it only binds to insoluble amyloid-β plaques [12], [28].

A phase 1 clinical trial found some evidence that Aduhelm reduces amyloid-β aggregation and slows the clinical progression of AD [12]. However, it is important to note that assessing the clinical symptoms of AD was not the primary focus of this study, and therefore these findings remain promising but inconclusive [12]. Following administration of Aduhelm, greater numbers of microglia were identified in close proximity to amyloid-β plaques, suggesting that Aduhelm may induce microglial phagocytic activity to facilitate amyloid-β clearance [12]. Similarly, a phase 2 clinical trial identified cognitive and functional benefits to Donanemab treatment in AD patients, as well as increased amyloid-β clearance [14]. These initial results suggest an incredibly promising future for amyloid-β monoclonal antibody treatments — so why is there such controversy surrounding the FDA approval process?



The Future of AD Research and Treatments

The FDA granted approval of Aduhelm via the accelerated approval pathway [29]. This pathway does not represent permanent approval, nor does it mean that the FDA views Aduhelm as a definitive cure for AD. What it does mean is that the FDA believes it has strong evidence that Aduhelm successfully targets an underlying, physiological cause of AD: in this case, amyloid-β plaques [29]. Because there are no other viable treatments targeting the underlying cause of AD, the FDA is allowing patients to start taking Aduhelm based only on its success in clearing amyloid-β [29]. What remains to be seen is whether or not its success in clearing amyloid-β translates into cognitive and functional improvements in AD patients. Biogen is currently conducting experiments to determine whether or not this is the case, and if Aduhelm's efficacy for treating the clinical symptoms of AD remains unproven, the FDA may revoke its approval. The accelerated approval pathway through which Aduhelm was approved rests on a basic assumption: ameliorating the underlying source of a disease will alleviate the associated clinical symptoms as well. It is a relatively valid assumption, although its accuracy likely varies based on how many factors are involved in the etiology of any given disease. AD is an extremely complex disease whose underpinnings remain incompletely understood after years of research. While this article has focused on the complexities associated with amyloid-β aggregation and neuroinflammation, there are other biological factors associated with AD including neurofibrillary tangles and loss of synaptic connections, not to mention the roles of genetics, environmental conditions, comorbidities, gender, nutrition, physical activity and so much more [30].

So will the clearance of amyloid-β plaques facilitated by Aduhelm reduce the clinical symptoms of AD? The short answer is maybe. Despite the extremely tangled web of contributing factors, amyloid-β does seem to play a large role in AD, and clearance of amyloid-β plaques may prove effective at alleviating the clinical symptoms of the disease. However, as previously discussed, amyloid-β plaques may be of secondary importance compared to soluble amyloid-β oligomers when it comes to AD onset and progression [18], [2]. It therefore remains to be seen whether or not the clearance of amyloid-β plaques will prove sufficient for alleviating the cognitive and functional symptoms of AD. If so, treatments such as Aduhelm and Donanemab would represent a major step forward in addressing one of the most pressing biomedical issues of our time.

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