Moving beyond the Aβeta hypothesis of Alzheimer's Disease

Monika Trzcinska, PhD and Darren Eskow, MBA

August 2019

The news surrounding Alzheimer's disease (AD) in the past several years has been much the same, but the reaction to the most recent clinical trial failure, as judged by the number of voiced opinions and publications, shows how much hope there has been that clearing the buildup of beta amyloid (Aβ), which makes up the senile plaques in the brain, would halt or at least slow the cognitive decline in AD patients. The Phase 3 failure of Biogen/Eisai monoclonal antibody, aducanumab, has, in the opinion of many, finally put the proverbial "nail in the coffin" of the Aβ hypothesis, the prevailing belief that the neurodegenerative process is a series of events triggered by the abnormal processing of the amyloid precursor protein (APP) and subsequent Aβ accumulation in the brain.

Aducanumab joins the list of passive immunotherapy* predecessor molecules (J&J's bapineuzumab, Roche's crenezumab, Pfizer's ponezumab or Eli Lilly's solanezumab) that appear to confirm a class effect (Table 1). Yet among the assets currently in Phase 3 development six are targeting Aβ protein inhibition, with Roche's gantenerumab, being assessed in prodromal and mild AD patients, leading the way. Additionally, Eisai, Biogen's partner, recently revealed that the company is progressing another Aβ antibody, BAN2401, which has a higher selectivity and specific binding to protofibrils, into Phase 3. Furthermore, the researchers from Germany's Jülich Research Centre reported that a new small molecule, PRI-002, which completed a Phase 1 trial, breaks down Aβ at the point at which it aggregates into oligomers. A few years ago we would be awaiting the results of these ongoing trials with great hope and anticipation, but having been disappointed so many times before, there is much more skepticism that these molecules will succeed in reducing the cognitive decline in AD patients.

*Note: *Passive immunization involves the administration of exogenous antibodies, while active immunization involves the stimulation of the immune system to produce its own antibodies via the administration of a vaccine.*

Table 1. List of late-stage monoclonal antibodies targeting Aβ peptides (AdisInsight May 2019, Spencer and Masliah, 2014, van Dyck, 2017)

Antibody	Company	Source and Isotype	Target	Target Population	Status
Aducanumab	Biogen/Eisai/Neurimmune	Human/IgG1	Oligomers, fibrils, plaques	Prodromal, mild AD (Phase 2); mild cognitive impairment (MCI) or mild AD (Phase 3)	Discontinued in 2019 (Phase 3)
BAN2401	Eisai/Biogen	Humanized/IgG1	Soluble protofibrils	Early AD or MCI (Phase 2); early symptomatic AD (Phase 3)	Phase 3 ongoing (expected readout in 2024)
Bapinezumab	Janssen/Pfizer	Humanized/IgG1	Fibrils, Plaques	Mild to moderate AD (Phase 2); mild to moderate Alzheimer's disease in ApoE4 carriers and noncarriers (two Phase 3)	Discontinued in 2012 (Phase 3)
Crenezumab	Roche/AC Immune	Humanized/IgG4	Monomers, oligomers, fibrils	Mild to moderate AD (Phase 2); prodromal, MCI AD (two Phase 3); continues to be assessed (Phase 2) in Alzheimer's Prevention Initiative in patients who have PSEN1 E280A autosomal-dominant mutation	Discontinued in 2019 (Phase 3); Prevention trial ongoing (Phase 2)
Gantenerumab	Roche/Chugai	Human (phage-derived)/IgG1	Fibrils, Plaques	Inherited autosomal-dominant mutation in APP, presenilin-1, or presenilin-2 (Phase 2/3); mild AD (Phase 3)	Phase 3 ongoing (expected readout in 2023)
Ponezumab	Pfizer/Rinat Neurosciences	Humanized/IgG2a	Monomers, plaques	Mild to moderate AD (Phase 2)	Discontinued in 2011 (Phase 2)
Solanezumab	Eli Lilly	Humanized/IgG1	Monomers	Mild to moderate AD (Phase 2); prodromal AD (Phase 3)	Discontinued in 2017 (Phase 3)

Other approaches at reducing Aβ production have been met with the same lack of success as the monoclonal antibodies. For example, Merck's verubestat and AstraZeneca's/Eli Lilly's lunabecestat were two β-secretase (BACE) inhibitors (molecules that cleave APP) that met the same fate as monoclonal antibodies targeting Aβ. Verubestat was not only ineffective, its administration was linked to worsening of cognitive symptoms. Similarly, Eli Lilly's semagacestat and BMS's avagacestat, two inhibitors of γ-secretase (part of the APP cleaving complex) were also found to be not only ineffective, but showed adverse events in clinical trials. This July, Amgen and Novartis announced the termination of their pivotal Phase 2/3 clinical trial for the BACE1 inhibitor, umibecestat. The patients taking umibecestat experienced a worsening rate of cognitive decline. Elenbecestat, Eisai's/Biogen's BACE inhibitor, however, is still in Phase 3 with the projected completion date of November 2023.

So how did we get here? The birth of the Aβ hypothesis can be linked to a seminal paper by Glenner & Wong, published in 1984. The authors reported that a purified protein derived from the twisted β-pleated sheet fibrils in cerebrovascular amyloidosis associated with Alzheimer's disease had been isolated. More than two decades of research then ensued, with the scientific evidence (including studies in several genetically-modified mouse models in which Aβ deposited in the brain led to a measurable cognitive impairment) supporting the Aβ hypothesis.

The Aβ peptide is generated by the proteolytic processing, with the help of β-, and γ-secretases, of a larger transmembrane protein APP. This means that the accumulation of Aβ in the brain is a race between its production and clearance. Most of the known >160 gene mutations in APP, presenilin 1 and presenilin 2 (transmembrane proteins involved in γ-secretase complex) that underlie some forms of early-onset (<60 years of age) autosomal-dominant familial AD increase the production of Aβ42 (the longer, more amyloidogenic form of the peptide). Consequently, approaches focused on modulating Aβ levels and particular isoforms of the Aβ42 peptide have been most intensely studied in the past decades. The majority of these studies have focused on the rationale that the reduction in Aβ production would lead to a decrease in the formation of Aβ and ultimately slow down or halt neurodegeneration.

Could all the years of animal research and encouraging Phase 2 results that were not recapitulated in Phase 3 trials be explained by poor patient selection, providing an intervention that is too late in the disease process, choice of agent used, dose of the chosen molecule and target engagement? Or is our understanding of the underlying biology of AD still too limited?

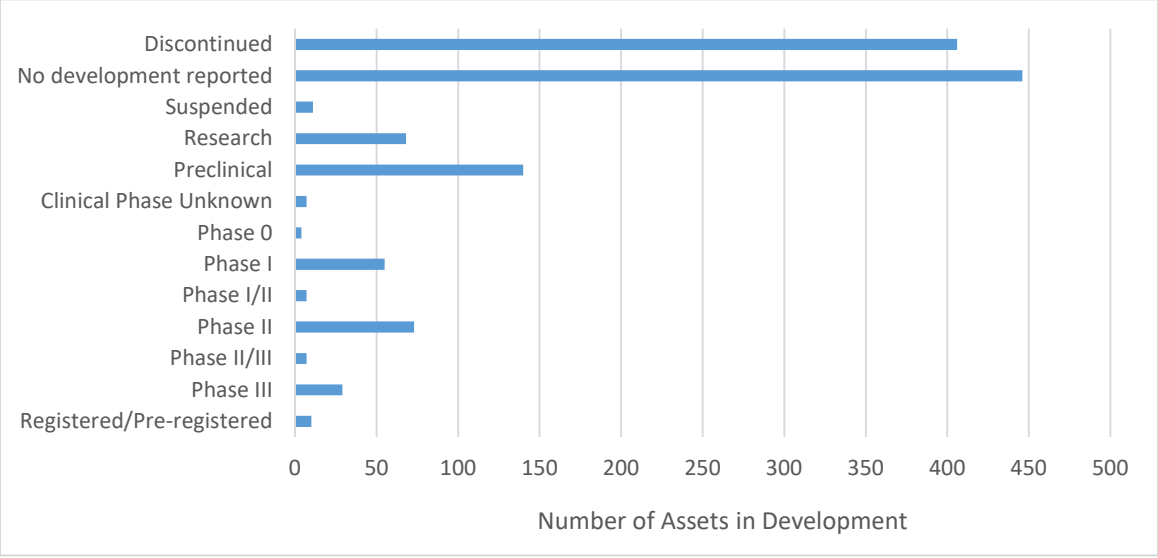
Indeed, there is evidence that runs contrary to the Aβ hypothesis. For example, there are many seemingly healthy individuals who have Aβ deposits, and there are diagnosed AD patients who show very few Aβ deposits. Furthermore, in the brains of elderly non-demented patients, the distribution of senile plaques is sometimes as extensive as that of dementia patients. This suggests that Aβ amyloid deposition is a phenomenon associated with aging, and has no direct relation with the onset of AD. Taking these facts into account, it appears that neuronal loss, the resulting neurodegeneration and amyloid deposition are independent, unrelated phenomena, contrary to the Aβ hypothesis and suggest that enhancing Aβ clearance could be equally as effective at lowering Aβ burden.

Despite most efforts having been centered on reducing Aβ production or accumulation and subsequent ability to slow the cognitive decline, molecules with other mechanisms of action have, however, also been unsuccessful in the clinic. Some of us recall the infamous Dimebon fiasco, when in 2010, after two large Phase 3 trials, this histamine H1 receptor inhibitor (which was also found to target L-type and voltage-gated calcium channels, AMPA and NMDA glutamate receptors, as well as α-adrenergic receptors and serotonergic receptors) failed to demonstrate changes in primary and secondary endpoints in an AD trial. Because Dimebon showed positive signals in preclinical animal models and one Phase 2 trial in Russia, there was much hope that it would also prove to be efficacious in larger Phase 3 trials. More recently, Lundbeck assessed idalopirdine, a potent and selective 5-HT_6 receptor antagonist in moderate AD patients, but that molecule also failed to meet its primary endpoints in three Phase 3 trials.

The number of clinical trials that have been discontinued or halted from development in AD demonstrates the complexity of the disease with which we are dealing (Figure 1). Specifically, between 1993 and 2015, more than a hundred potential medicines for Alzheimer's were stopped from progressing through clinical trials, and only seven were approved in the U.S. All provide symptomatic relief with no impact on disease progression and predominantly center on two biologic mechanisms, prolongation of the acetylcholine signal at the synapse via the inhibition of its breakdown and the inhibition of the glutamate neurotransmission:

- Aricept (donepezil, an acetylcholinesterase inhibitor), approved in 1996 for early, moderate and severe AD
- Cognex (tarcine, an acetylcholinesterase inhibitor), approved in 1993 for early to moderate AD
- Exelon (rivastigmine, an acetylcholinesterase and butyrylcholinesterase inhibitor), approved in 2000 for early to moderate AD
- Namenda (memantine, an N-methyl-D-aspartate receptor antagonist), approved in 2003 for moderate to severe AD
- Namenda XR (extended release of memantine), approved in 2010 for moderate to severe AD
- Namzaric (combination of memantine and donepezil), approved in 2014 for moderate to severe AD
- Razadyne/Reminyl (galantamine, an acetylcholinesterase inhibitor), approved in 2001 for early to moderate AD

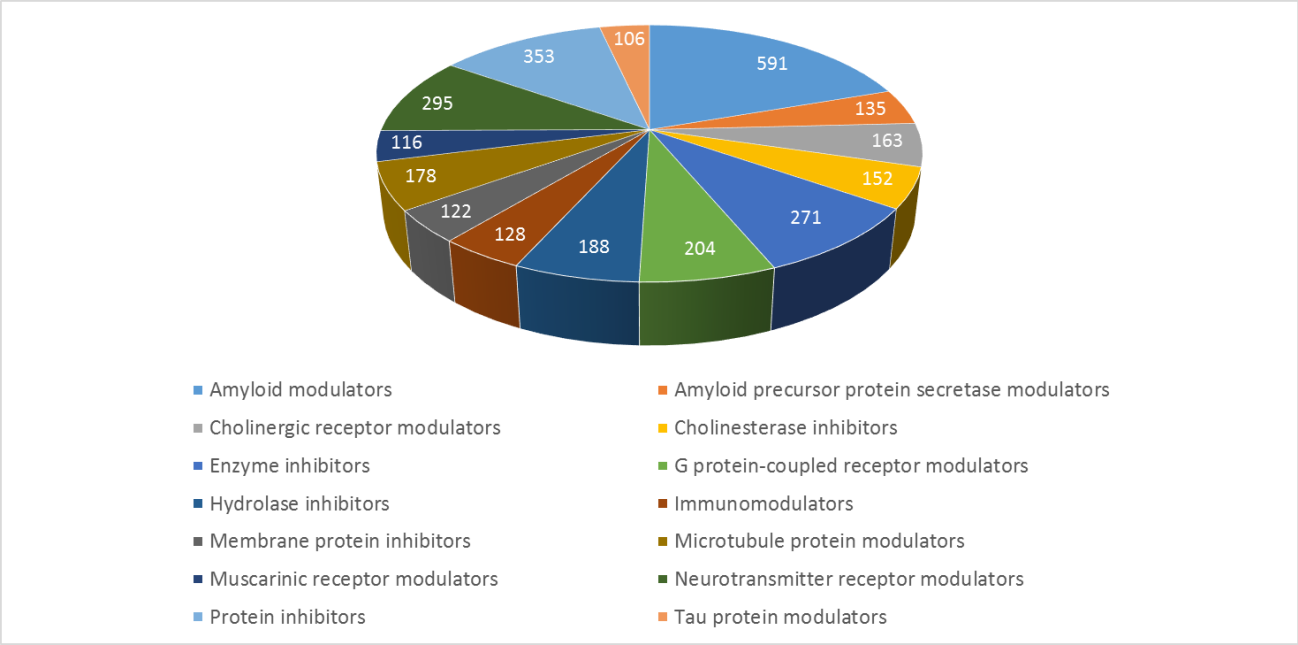
Figure 1. Number of assets in development for the potential treatment of AD; mid- to late-stage pipeline is sparse with many programs having been discontinued, halted from development or suspended (AdisInsight, May 2019)



As an industry, we spent an estimated $5.7 billion per AD program, with each Phase 2/3 alone carrying the ~$2.83 billion price tag, and we still have nothing to show for it. While we voice our frustrations and regroup around the validity of other biological targets, the clock is ticking as the world's population of AD dementia increases steadily from 35 million today to an estimated shocking 135 million in 30 years. It will cost the healthcare system in the US alone $1.1 trillion by the year 2050 to manage these patients, assuming there is no disease-modifying treatment approved by then.

But perhaps the tides are slowly beginning to turn. Despite the fact that more than 700 assets at various stages of development are Aβ or APP modulators, the pipeline shows an impressive number of early stage molecules in development targeting other biological mechanisms, some of which have not been previously studied in the clinic in any great detail (Figure 2).

Figure 2. Number of assets in AD pipeline by the biological targets being pursued. Amyloid or amyloid precursor protein modulators continue to lead the way, followed by protein inhibitors and neurotransmitter receptor modulators (AdisInsight, May 2019)



In addition, when taking a closer look at the agreements executed in the past five years for molecules targeting AD (Table 2), it is obvious that AD continues to be worthy of investment. At the time of these transactions licensors were willing to pay on average $93 million in upfront fees, $341 million in milestones for the total average deal value of $744 million. Even if only one of the currently ongoing mid- to late-stage trials targeting one of the biological mechanisms is able to demonstrate an inkling of efficacy in Phase 3, it would re-invigorate the entire field and stimulate additional investments needed to support our unrelinquished belief that a curative approach to AD is still within our reach.

As we continue to pursue the holy grail of one molecule as a disease-modifying agent, we also need to ask ourselves whether the pursuit of a monotherapy in a complex multifactorial disease like AD is valid. To date, beyond Namzaric, limited data exists for the effectiveness of drug combinations in AD. However, the numerous notable failures in AD have stimulated a multi-target-directed ligands strategy, which is gaining some recognition as a way to explore repurposing of known drugs (e.g.: rasagiline and liraglutid), or to create new pharmacophores based on existing molecules with the help of structure-based, in silico, and data-mining approaches (e.g.: resveratrol and clioquinol). Furthermore, as we are working towards a disease-modifying treatment, perhaps there are also opportunities to not only improve symptom management, but to address co-morbidities associated with AD, such as depression, agitation, sleep disturbances and psychotic symptoms.

Probably no other biological mechanism has gotten as much attention as the Aβ hypothesis. The time has come to refocus our efforts on other areas of biology and potentially move away from a single target/one molecule approach. We can learn a great deal from copious clinical and preclinical data available so that we can have a better shot at developing treatments that can actually move the needle in this debilitating disease.

Table 2. List of AD licensing transactions with disclosed values executed in the past five years (Source: UpToDate, May 2019)

Date of Deal Announced	Trade Name	Mechanism of Action	Indication	Current Phase of Development	Licensor	Licensee(s)	Type	Upfront Payment ($ m)	Other considerations ($ m)	Total Deal Value ($ m)
18-Dec-18	BPN14770	phosphodiesterase-4D (PDE4D) allosteric inhibitor	Fragile X Syndrome, Alzheimer's disease and other indications marked by cognitive and memory deficits	Phase 2 ongoing	Tetra Discovery Partners Inc	Shionogi & CO., LTD	Commercialization; Development (Japan, Taiwan and Korea)	5	35 in equity Investment	160
7-Sep-17	LYN-057	once weekly formulation of memantine hydrochloride	Alzheimer's disease	Phase 1 completed	Lyndra Therapeutics, Inc	Allergan plc	Co-development (includes other modified release molecules)	15	90 in development and regulatory milestones	105
13-Apr-17	Gosuranemab (BIIB-092, BMS-986168)	humanized IgG4 monoclonal anti-tau antibody	Progressive Supranuclear Palsy and Alzheimer's disease	Phase 2 ongoing	Bristol-Myers Squibb	Biogen Inc.	Exclusive commercialization; Exclusive development (global rights)	300	410 in development and regulatory milestones	710
6-Apr-16	HTL0016878; HTL0018318	M1 and M4 muscarinic receptor agonists	Psychosis associated with Alzheimer's disease and other neurologic disorders	Phase 1 ongoing; Phase 1b suspended	Heptares Therapeutics	Allergan plc	Exclusive commercialization; Exclusive development (global rights)	125	665 in development and regulatory milestones; 50 USD in R&D and 2,500 USD in sales milestones	3,340
12-Jan-15	ACI-35	liposome-based vaccine of 16 copies of phosphorylated tau on residues S396 and S404 anchored into a lipid bilayer	Alzheimer's disease	No development reported post Phase 1	AC Immune SA	Janssen Pharmaceuticals, Inc.	Commercialization; Development (global rights)	Undisclosed	Undisclosed	509
16-Sep-14	MEDI-1814	antibody selective for Aβ42	Alzheimer's disease	Phase 1 suspended	AstraZeneca PLC	Eli Lilly and Company	Co-commercialization; Co-development (global rights)	Undisclosed	Undisclosed	500
24-Jun-14	BNC375	positive allosteric modulators (PAMs) of the α7 nicotinic acetylcholine receptor (nAChR)	Alzheimer's disease and other neurological indications	No development reported post Phase 1	Bionomics Ltd.	Merck & Co., Inc.; Roche Holding AG	Commercialization; Development; Evaluation (global rights)	20	506 research and clinical milestones	526
21-May-14	Memtin	Leptin analog	Alzheimer's disease and other cognitive disorders	Phase 2-ready, but no development reported	Neurotez, Inc.	Gca Therapeutics, Ltd.	Exclusive commercialization; Exclusive development (China, exclusive of Hong Kong, and Taiwan)	Undisclosed	Undisclosed	102.5
Average								**93**	**341.2**	**744**

References

Alzforum, https://www.alzforum.org

Bright Focus Foundation, https://www.brightfocus.org/alzheimers/article/treatments-alzheimers-disease

Cummings, J., et al. (2018a). Alzheimer's disease drug development pipeline: 2018. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 4:195.

Cummings, J., et al. (2018b). The price of progress: Funding and financing Alzheimer's disease drug development. Alzheimer's & Dementia: Translational Research & Clinical Interventions 4: 330.

Glenner, G.G and Wong, C.W. (1984). Alzheimer's disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochemical and Biophysical Research Communications, 120:885.

Hughes, R.E., et al. (2016). One for all? Hitting multiple Alzheimer's Disease targets with one drug. Frontiers in Neuroscience, 10: 177.

Kametani, F and Hasegawa, M (2018). Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. Frontiers in Neuroscience, 12:1.

Mao, F, et al. (2014). New multi-target-directed small molecules against Alzheimer's disease: a combination of resveratrol and clioquinol. Organic and Biomolecular Chemistry, 31: 5936.

Mehta, D., et al. (2017). Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010–2015. Expert Opinion in Investigational Drugs, 26:735.

Morris, G.P. et al., (2014). Inconsistencies and Controversies Surrounding the Amyloid Hypothesis of Alzheimer's Disease. Acta Neuropathologica Communications, 2:135

PhRMA, "Medicines in Development for Alzheimer's Disease" 2017 Report. https://www.phrma.org/report/medicines-in-development-for-alzheimer-s-disease

PhRMA, "Researching Alzheimer's Medicines: Setbacks and Stepping Stones," Summer 2015. http://phrma-docs.phrma.org/sites/default/files/pdf/alzheimers-setbacks-and-stepping-stones.pdf

Ramsay, R.R., et al. (2018). A perspective on multi-target drug discovery and design for complex diseases. Clinical and Translational Medicine, 7:3.

Scott, T.J. et al. (2014). Economic analysis of opportunities to accelerate Alzheimer's disease research and development. Annals of the New York Academy of Sciences, 1313:17.

Selkoe, D.J and Hardy, J (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine, 8:595.

Spencer, B and Masliah, E. (2014). Immunotherapy for Alzheimer's disease: past, present and future. Frontiers in Aging Neuroscience, 6:1.

Tanzi, R.E., et al. (2004). Clearance of Alzheimer's Aβ Peptide: The Many Roads to Perdition. Neuron, 43:605.

Technology Networks, "Using Therapeutic Antibodies Against Alzheimer's Disease", 2018. https://www.technologynetworks.com/drug-discovery/articles/using-therapeutic-antibodies-against-alzheimers-disease-309953

Van Dyck, C.H (2017). Anti-Amyloid-b Monoclonal Antibodies for Alzheimer's Disease: Pitfalls and Promise. Biological Psychiatry, 83:311.