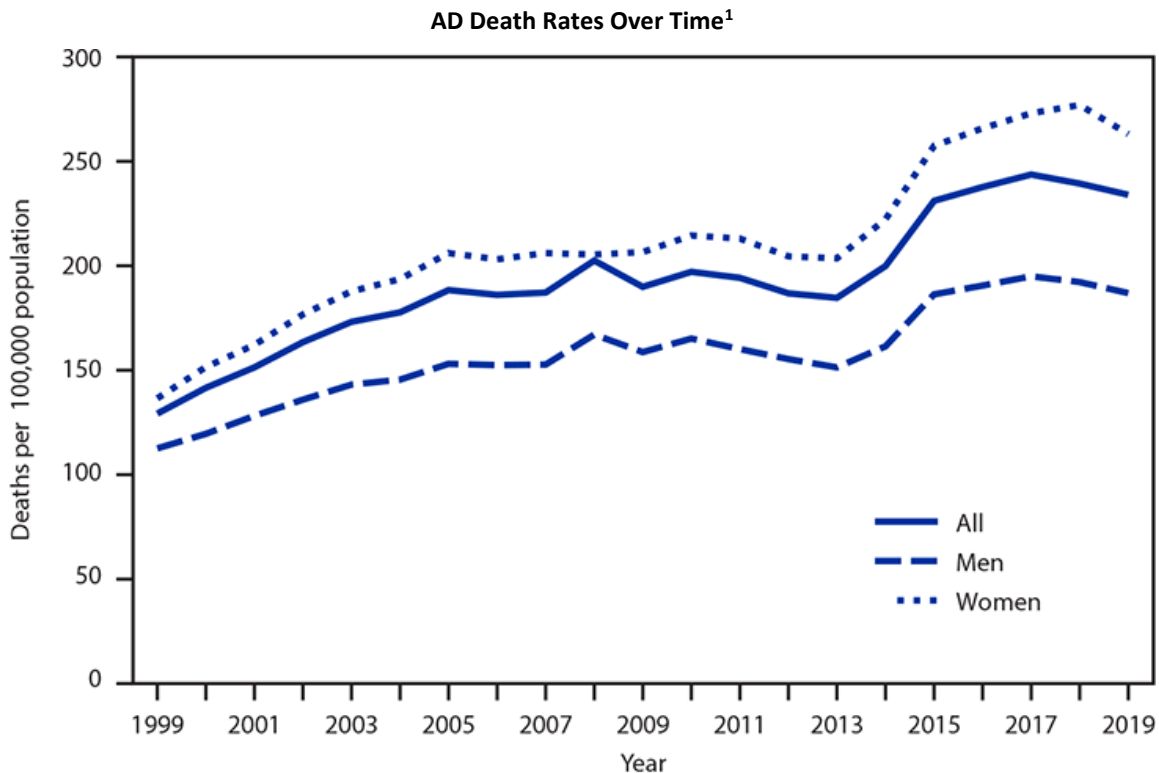


More Specificity is What the Doctor Ordered

Alzheimer's disease (AD) is one of human health's most relentless adversaries. In just a few years it is expected to be the highest cost disease Americans face, overtaking heart disease and cancer. One of the driving factors for this shift is that, in contrast to headway made against heart disease and cancer, no disease modifying therapies have emerged to fight it. It is the only top ten cause of death without a cure.

The last few years have been [dramatic ones](#) for the most prominent candidate in AD, Biogen's (NASDAQ: BIIB) Aduhelm. With an early termination of a Phase III trial in early 2019 and a tumultuous reversal of fortunes over the next twenty-seven months, Biogen's monoclonal antibody (mAb) was eventually approved by the FDA in June 2021. Aduhelm was the first drug approved for Alzheimer's disease in almost two decades and followed hundreds of failures. While the drug did not yield the benefits many desired, it did provide hope for patients and confidence that the agency will approve prospects that can meet surrogate endpoints in areas of unmet need. The success of Aduhelm with the FDA provides a template for the next generation of neurodegenerative agents that can build on the achievements of predecessors.



¹ QuickStats: Age-Adjusted Death Rates for Alzheimer Disease Among Adults Aged ≥65 Years, by Sex — National Vital Statistics System, United States, 1999–2019. MMWR Morb Mortal Wkly Rep 2021;70:602. DOI: <http://dx.doi.org/10.15585/mmwr.mm7016a5external icon>

First Generation A β AD Candidates

mAbs that were developed over the last decade and a half were mostly non-specific as to the type of amyloid β they targeted and frequently produced inflammatory side effects. Some efficacy was observed in early trials, but the signal for most of these candidates was not strong enough to pass the registrational test. Aduhelm and other drugs in the same generation of amyloid β targeting such as bapineuzumab and solanezumab were heralded as the vanguard of the group. Not only did these mAbs bind to toxic oligomers, which have strong scientific support as the cause of AD, but also to monomers and plaques. The lack of specificity had a few consequences, namely dilution of the mAb via monomer and plaque binding and potentially fatal swelling in the brain.

Now that we have the benefit of experience from a long list² of candidates in advanced trials, next generation approaches can build on our accumulated knowledge. First generation disease modifying therapies targeting amyloid β were not selective enough. Not only did they bind to toxic amyloid β oligomers, but also to other forms of the peptide. This led to withdrawals, failures and controversial drug approvals and the lack of a product that has proven itself to slow or stop dementia. Rather than lead the medical community into the depths of despair, these hurdles have inspired it to redouble its efforts and untie the tangles.

Second Generation Candidates

Many in the neurodegenerative space recognized that early amyloid β -targeting Alzheimer's drugs could bind to toxic oligomers; however, they were also distracted by binding to other helpful or harmless forms of amyloid β . To remedy this distraction, successful candidates must selectively bind only to toxic oligomers, the true target.³ They should also avoid binding to plaques and vascular deposits which contributes to vasogenic edema and microhemorrhages, better known as [amyloid related imaging abnormality](#) (ARIA-E and ARIA-H). The presence of the ARIA side effects restricted the amount of mAb that could be administered and also limited the amount of drug available to sequester and target misfolded toxic oligomers for destruction. Soluble oligomers are believed to be most toxic to neurons and to be responsible for memory loss and neuronal death.⁴

Immunoglobulin G (IgG) 1-4

Each of the successful next generation candidates will present a mechanism of action targeting toxic oligomers; however, different immunoglobulin G (IgG) backbones are used to achieve this end. IgG is the most common type of Ig found in blood circulation and is responsible for many humoral immune responses, including effector function. Effector functions include neutralizing harmful molecules, activating the complement pathway and cell lysis, and triggering phagocytosis and inflammation. The

² 1st generation candidates that moved into advanced trials but were not approved include elenbecestat, lanabecestat, crenezumab, ponezumab, azeliragon, verubecestat, intepirdine, idalopirdine, bryostatin & azeliragon. This is not a comprehensive list of all the candidates but does provide a representative selection that next generation agents can build upon to improve prior shortcomings.

³ Cline, E. *et al.* The Amyloid- β Oligomer Hypothesis: Beginning of the Third Decade. *J Alzheimers Dis.* 2018; 64(Suppl 1): S567–S610. Published online 2018 Jun 12. Prepublished online 2018 May 18.

⁴ Hong, W., Wang, Z., Liu, W., O'Malley, T. T., Jin, M., Willem, M., Walsh, D. M. (2018). Diffusible, highly bioactive oligomers represent a critical minority of soluble A β in Alzheimer's disease brain. *Acta Neuropathologica*, 136(1), 19–40. doi:10.1007/s00401-018-1846-7

IgG is composed of four subclasses, IgG 1 through 4, that differ with respect to their effector function. A number of factors impact the level of the effector function but in general IgG1 and IgG3 have higher levels of activity while IgG2 and IgG4 have lower levels. When interacting with plaque and vascular deposits of amyloid β , antibodies with effector function can trigger mechanisms that cause inflammation and ARIA as observed in clinical trials. However, when there is no plaque binding, the risk of this side effect is minimal and the effector function promotes clearance of antibody-marked oligomers by microglia more efficiently than with IgG2 or IgG4 which possess little effector function.

The Front-Runners

Several new candidates that appear to offer better specificity and selectivity and also avoid ARIA are now emerging into later stages of development. Three candidates that stand out the most include Eli Lilly's (NYSE: LLY) donanemab, Acumen Pharma's (NASDAQ: ABOS) ACU193 and ProMIS Neurosciences' (TSE: PMN.TO) PMN310, each of which addresses the main disadvantages of earlier amyloid β targeting mAb.

Donanemab

[Lilly's donanemab](#) is a humanized IgG1 mAb which is differentiated from other amyloid β approaches by its use of pyroglutamate as a target. Pyroglutamate appears at the N-terminus of amyloid β peptides and is a target for mAbs given its unique epitope. It is a natural amino acid derivative and is participates in an intermediate step in the production of glutathione, a potent anti-oxidant. Pyroglutamylated amyloid β is associated with amyloid β misfolding into more toxic aggregates,^{5,6} accelerates the aggregation of amyloid β ⁷ and can also be found in plaque.

Eli Lilly is conducting a [Phase III trial](#) investigating donanemab in an ongoing randomized, placebo-controlled, double-blind, multi-center study. Lilly has started a rolling submission of a BLA to the FDA based on success of its Phase II trial that [showed](#) an improvement in cognition and daily function in patients that took the drug. Donanemab may receive approval by the second half of 2022.

ACU193

[ACU193](#) is a humanized IgG2 mAb in development by [Acumen Pharmaceuticals](#). It selectively binds to soluble amyloid β oligomers. The candidate is enrolling Alzheimer's patients with mild cognitive impairment or mild dementia in a Phase I clinical trial designated [INTERCEPT-AD](#). Preclinical studies in a mouse model demonstrated behavioral deficits improvements in [open field](#) and maze evaluations. These non-clinical data support the toxicity of amyloid β oligomers and the selective binding of ACU193 to these proteins.

The [Phase I study's](#) primary goal is to determine safety and proof of mechanism. The trial is also comparing ACU193 against patients in a placebo arm which may provide cognition and biomarker data.

⁵ Galante D, *et al.* A critical concentration of N-terminal pyroglutamylated amyloid beta drives the misfolding of Ab1-42 into more toxic aggregates. *Int J Biochem Cell Biol.* 2016 Oct; 79():261-270.

⁶ Perez-Garmendia, R., Gevorkian, G. Pyroglutamate-Modified Amyloid Beta Peptides: Emerging Targets for Alzheimer's Disease Immunotherapy. *Current Neuropharmacology*, 2013, 11, 491-498

⁷ Lee J, *et al.* Role of the fast kinetics of pyroglutamate-modified amyloid- β oligomers in membrane binding and membrane permeability. *Biochemistry.* 2014 Jul 22; 53(28):4704-14.

PMN310

Another next-generation candidate that exhibits specificity and minimizes the risk of ARIA-E is on the cusp of starting a Phase I study. [ProMIS Neurosciences](#)' lead candidate, [PMN310](#), is preparing for a Phase I clinical trial, with completion of IND-enabling work targeted for the second half of 2022. The study will begin after a successful investigational new drug (IND) submission. PMN310 uses the IgG1 isotype backbone, which is in contrast to ACU193's IgG2 isotype. IgG1 has effector function, which promotes clearance of unwanted amyloid β , with minimal concern regarding ARIA since PMN310 does not bind to plaques. The nominal risk of ARIA will also allow higher dosing and potentially better efficacy than predecessors.

ProMIS differentiates itself from its neurodegenerative peers with its discovery platform⁸ which identifies epitopes unique to misfolded proteins, allowing for target specificity. Its antibodies have demonstrated selective binding to oligomers and maintenance of short term memory in an animal model.

Summary

The Alzheimer's disease space has experienced many ups and downs over the last few years, with desperation followed by hope. It has also provided a base of knowledge that can be used to develop the next generation of amyloid β -targeting disease modifying therapies. Beyond identifying the right form of amyloid β , the next generation of Alzheimer's therapies should also benefit from earlier intervention, improved biomarkers and inflammation control. The latest crop of candidates including Lilly's donanemab, Acumen's AC193 and ProMIS' PMN310 have built upon the shoulders of those that came before and are expected to make headway against this difficult disease.

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<sup>8</sup> The computational platforms are called ProMIS and Collective Coordinates.