Beyond amyloid: What's next for Alzheimers disease therapeutics?

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27 March 2023

Bradlee Heckmann, PhD, from USF Health Neuroscience Institute, Byrd Alzheimer's Center & Asha Therapeutics, in this discussion goes beyond amyloid, asking what's next for Alzheimer's Disease therapeutics

The recent approvals of aducanumab and lecanamab, targeting amyloid beta, a key pathogenic hallmark of Alzheimer's Disease (AD), represent an impressive step forward in developing new treatment options for one of the most devastating neurological diseases. AD impacts over 5 million individuals in the United States and an estimated 20-24 million people globally. Moreover, AD represents the sixth leading cause of death and according to the Alzheimer's Association approximately one in three individuals will die with either AD or a related dementia. [(1)]

What are Alzheimer's Disease therapeutics?

AD is a progressive, incurable neurodegenerative condition characterized by dementia and overall mental deterioration leading to deficiencies in memory, speech, language, and ultimately death. AD is pathologically characterized by the deposition of aggregated proteins called amyloid beta within the brain, forming structures known as amyloid plaques. These amyloid plaques have long been considered primary drivers of AD pathology. For this reason, many Alzheimer's Disease therapeutics programs have focused on targeting amyloid beta and amyloid plaques. Drugs including aducanumab and lecanamab are excellent examples of amyloid-targeting therapeutics. From a biological viewpoint, neutralizing amyloid pathology would be of logical benefit to reducing AD pathology and symptoms. Unfortunately, although these drugs represent an immense progression in AD therapies, they do not display the broad sweeping efficacy that was originally hoped for. During clinical trials, lecanamab was significantly more efficacious than aducanumab slowing clinical decline by 27% after 18 months of treatment [(2)]. It is important to reiterate that this level of effect has not been seen with any Alzheimer's Disease therapeutics to date. Again, it is substantial progress in therapeutic options, but AD remains incurable.

While drugs, including lecanamab and other amyloid therapies, are showing promise both in preclinical studies and now in the clinic, the disease persists. Is targeting amyloid the end of all of AD? Based on clinical evidence today, it's an excellent start but certainly not the means to an end. Therefore, the question becomes, what's next?

Do we simply try and improve amyloid therapies? I and many others argue for a complementary pathway alongside amyloid therapies. Many other cellular pathways are now implicated in the pathogenesis of AD and other neurodegenerative conditions, for that matter. Three pathways centric to brain function that are either altered or activated in AD are 1) tau pathology, 2) neuroinflammation, and 3) mitochondrial dysfunction. These pathways were long overlooked as they typically are activated or contribute to AD only after amyloid deposition has already begun years prior. However, new evidence suggests that targeting them could significantly benefit therapeutically.

Tau pathology in Alzheimer's disease

The first is tau pathology. Tau is a normal protein that helps to maintain the function of nerve cells (neurons). In AD, tau becomes chemically modified in a process called phosphorylation which destabilizes tau and leads to neuronal dysfunction and, eventually, neurodegeneration. Genetic studies show preventing this tau pathology from occurring can preserve neuronal function. Pharmacological targeting of tau has proven to be more challenging as there are many 'flavors' of tau, and the proteins that become activated and phosphorylate tau in AD have either been poorly defined or drugs designed to target them have proven promiscuous in nature, resulting in off-target, or unwanted effects. However, new breakthroughs are on the horizon, with new tau immunotherapies entering clinical trials.

The risks of neuroinflammation

The second pathway of potential Alzheimer's Disease therapeutics value is neuroinflammation. In AD, chronic neuroinflammation is known to promote continued neuronal dysfunction, propagation of tau pathology, and activates cell death and neurodegeneration. New pathways that regulate neuroinflammation have recently been identified, including LC3-associated endocytosis or LANDO [3-5]. LANDO-deficiency promotes neuroinflammation and, in models of AD, leads to a robust exacerbation of AD pathology, including neurodegeneration and memory impairment.

Studies using human AD brain samples show the LANDO machinery, along with the autophagy machinery, a cellular homeostasis pathway, are reduced and may contribute to increased inflammation in the AD brain. While re-expressing a whole pathway of regulatory proteins, including those that control LANDO, is not therapeutically viable at present, it is possible to target neuroinflammation. Various novel inflammatory inhibitors are being developed, targeting key inflammatory pathways related to AD, including the NLRP3 inflammasome. Optimistically, we will see compounds targeting neuroinflammation in clinical trials for AD and other neurodegenerative conditions in the coming years.

Regulation of mitochondrial function

The third pathway, which represents a significant Alzheimer's Disease therapeutics opportunity, is in the regulation of mitochondrial function. Mitochondria are the energy-producing organelles of the cell, and, even more so, are centric signaling hubs for a whole host of cellular communications. The role of dysfunctional mitochondria has been well-characterized in the context of Parkinson's Disease (PD) and is now coming to light as a key contributor to AD pathogenesis. In AD, mitochondria can become fragmented, leading to failure in energy production, signaling and calcium homeostasis, a critical component to neuronal function. This can lead to increased neuroinflammation, direct nerve cell dysfunction and loss of signaling. Furthermore, it can directly promote the activation of cell death pathways. Targeting and restoring dysfunctional mitochondria may be the next breakthrough approach to treating AD by restoring cellular function, reducing inflammation, and limiting cell death activation.

What's next for Alzheimer's Disease therapeutics?

New therapies are on the horizon, and time will tell if targeting any of these alternative pathways will be of benefit in AD. However, I remain optimistic that the new therapies of tomorrow, paired with those showing great promise in clinics today, will be the means to end Alzheimer's Disease.

References

1. Alzheimer's Association. https://www.alz.org/alzheimers-dementia/facts-figures. (2022).
2. C. H. van Dyck et al., Lecanemab in Early Alzheimer's Disease. N Engl J Med 388, 9-21 (2023).
3. A. D. Rickman, A. Hilyard, B. L. Heckmann, Dying by fire: noncanonical functions of autophagy proteins in neuroinflammation and neurodegeneration. Neural Regen Res 17, 246-250 (2022).
4. B. L. Heckmann et al., LC3-Associated Endocytosis Facilitates beta-Amyloid Clearance and Mitigates Neurodegeneration in Murine Alzheimer's Disease. Cell 178, 536-551 e514 (2019).
5. C. Pena-Martinez, A. D. Rickman, B. L. Heckmann, Beyond autophagy: LC3-associated phagocytosis and endocytosis. Sci Adv 8, eabn1702 (2022).

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