ALZHEIMER'S DISEASE STATE OF PLAY

WITH FOCUS ON

SIMILARITIES BETWEEN MECHANISMS OF ACTION OF NE3107[1], XPRO[2], SIMUFILAM[3] AND COYA 301/302[4]

EXECUTIVE SUMMARY

Introduction: Alzheimer's disease and the search for treatments

Alzheimer's disease is the sixth leading cause of death in the United States and is estimated to affect 6.2 million Americans age 65 and older. The global Alzheimer's market is expected to reach $13.7 billion in 2030, making it potentially the largest unmet medical need.

Though the causes of Alzheimer's disease are probably different for each individual, main hallmarks and causes can be identified. The research note discusses amyloid, hyperphosphorylated tau, inflammation as a more novel hallmark of neurodegenerative diseases, and the cumulative burden of stressors due to Western lifestyle, metabolic syndrome, toxins and viruses as probable cause of neurodegenerative diseases

Traditional treatment consists of administration of acetylcholinesterase inhibitors, such as donepezil, galantamine and rivastigmine. Donepezil was first approved in 1996, or more than twenty years ago. These are symptomatic treatments and do not affect disease progression.

What followed were decades of trial failures. However, the times appear to be changing, both from a traditional as from a more novel view on Alzheimer's and the treatment thereof. The traditional view is based on the removal of amyloid, the more novel view is based on inflammation and metabolic dysregulation as culprits of Alzheimer's disease.

Recent moderate successes from anti-amyloid antibodies: Eisai/Biogen and Eli Lilly

Recent Phase 3 successes coming from anti-amyloid antibodies have been reported by Eisai/Biogen and Eli Lilly. The efficacy reported so far is modest; Eisai/Biogen's Leqembi and Eli Lilly's donanemab seem to allow for maximally a 25-40% slowing of cognitive decline, in milder stages of disease. Additionally, quite some side effects have been reported, including ARIA-E. The advent of anti-amyloid antibodies does not mean the large unmet medical need for the treatment of Alzheimer's disease has been met. Efficacy of treatments should improve, combination therapies should be considered whether or not focused on the biology of aging, side effects can be reduced, and further-advanced patient groups should be able to receive treatment as well. It will also remain to be seen whether, after the commercial failure of the first anti-amyloid antibody Aduhelm in light of

[1] Drug candidate of BioVie.
[2] Drug candidate of INmune Bio.
[3] Drug candidate of Cassava Sciences.
[4] Drug candidate of Coya Therapeutics.

accelerated approval controversy, cost and side effects, Leqembi and potentially donanemab are set to become commercial successes.

Similar further-reaching results: BioVie, INmune Bio, Cassava Sciences, Coya Therapeutics

Since 2021, four publicly listed companies have reported separate sets of data that seem to indicate that the progression of Alzheimer's disease can be stopped or even reversed, with an early onset and without side effects. For their respective drug candidates, BioVie, INmune Bio, Cassava Sciences and Coya Therapeutics, these companies share outspoken similar ambitions to stabilize or improve cognition in Alzheimer's disease.

Their respective drug candidates NE3107, XPro, simufilam and Coya 301/302 share more than a few similarities, among others with regards to their mechanisms of action, onset and safety profile. The author believes these similarities are not coincidental and merit further study to analyze whether the results are legitimate, reproduceable and sustainable. An analysis of the mechanistic rationale for the drug candidates of these different companies and an understanding of the value of biomarkers in AD may provide insights and validation of the new approaches which the author considers to have anti-inflammation and metabolic dysregulation as their common denominator.

As to anti-inflammatory treatments for Alzheimer's, there is a multitude of metadata-based publications showing the benefit of traditional TNF-inhibitors in the prevention of Alzheimer's. These TNF-inhibitors, however, are non-brain-penetrant and non-selective. As chronic neuroinflammation and neurodegeneration are inextricably linked to pro-inflammatory and detrimental activity of the brain's immune cells or glia, which are as abundant in the brain as the neurons themselves, rebalancing their activity may be essential in preventing, slowing down or even improving Alzheimer's. Selective inhibition of pro-inflammatory factors may be a key to success, as entire inhibition of TNF and/or TNFR2 signaling may present a further risk.

Similar data exists with regards to anti-diabetic treatments.

The respective drug candidates of the afore-mentioned companies may all exert anti-inflammatory activity through TLR4 and possibly CD14, through inhibition of ERK and JNK, through inhibition of NF-kB and through improved insulin sensitization. They appear to all have the potential to stabilize or even improve cognitive decline, through a process of systemic normalization which may be linked to the biology of aging. without the requirement for lengthy intravenous uptake.

The drug candidates of the afore-mentioned companies have a seemingly safe profile, without serious side effects, and seem to have a much faster onset than anti-amyloid therapies.

There are also differences between these respective drug candidates. For example, whereas NE3107 and XPro smay reduce inflammation through the inhibition of pro-inflammatory TNF signaling, simufilam may do so among others through the a7nAChR receptor. Coya pursues a similar goal with a different treatment, in an effort to rebalance the immune system by modulating regulatory T cells.

Each of these companies comes with different risks on their paths to success, which the research note efforts to discuss in detail. Those risks include, among others, risks related to litigation, administrative burden, and trial design.

Among several further insights mentioned in the research note, the following are highlighted.

BioVie's Phase 3 trial has enrolled patients with mild to moderate Alzheimer's disease, and at first sight has not based its trial design on the biology of patients. However, baseline data for its Phase 3 trial suggest that the biology of patients enrolled does match the drug's mechanism of action, which could de-risk that Phase 3 trial. That trial is slated to report topline data in the October-November 2023 timeframe.

INmune Bio's Phase 2 trial of XPro in Alzheimer's is ongoing, but would benefit from a US-related hold being lifted.

Cassava Sciences' Phase 3 trials are large and ongoing, slated to report topline data some time in 2025. Patients with mild Alzheimer's seem to benefit strongly from simufilam after 12 months of treatment. The author's calculation of the cognitive decline in patients with moderate Alzheimer's disease, on the basis of the recent data reported from a placebo-controlled Cognition Maintenance Study, shows that these patients' cognitive decline was faster than patients on placebo. This could put Cassava Sciences' Phase 3 trials at risk of not showing statistical significance.

Coya Therapeutics reported stabilization or improvement of cognition on various rating scales. The author's view is that further efficacy could be seen if Coya 301 were to be used in combination with another treatment (e.g. Coya 302, as tested in ALS).

Biomarkers

An understanding of the different biomarkers reported by the afore-mentioned companies, and a comparison with data reported from successful anti-amyloid antibody therapies, may allow for knowledgeable decisions as to efficacy and the potentially disease-modifying character of the concerned therapies. The research note has compiled and compared biomarker data reported from three anti-amyloid antibodies and those reported by BioVie, INmune Bio, Cassava Sciences and Coya Therapeutics. Several biomarkers have been highlighted, and particular attention has been given to NfL, a biomarker that has recently gained attention.

Investor potential

Positive reporting of placebo-controlled trials in Alzheimer's generally coincides with the additional of +10/+20 billion market value gains in the concerned (big pharma) companies, and substantial market value gains for related companies. Assuming, in case of success, the market value gains for each of these companies would be in between $5-$10 billlion, which appears reasonable taking into account Cassava Sciences' historical market cap of almost $5 billion after the reporting of open-label Phase 2 results, the potential gain related to Alzheimer's disease alone may be immense, e.g. in between ~6x-~250x depending on the respective company and a respective $5-$10 billlion market cap. The market caps of the concerned companies at the time of writing were as follows.

Company	Market cap	Trial stage
Cassava Sciences	$ 830 million	3
BioVie	$ 170 million	3
INmune Bio	$ 150 million	2
Coya Therapeutics	$ 40 million	/ * (Phase 2 ALS to start soon, academic Phase 2 in AD ongoing).

The goal of this research note is to provide insights in the potential of any of these drug candidates, and their respective risks. Like any research, it may be prone to errors, and is not exhaustive.