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Analyst Coverage

ALZHEIMER'S DISEASE STATE OF PLAY

WITH FOCUS ON SIMILARITIES BETWEEN MECHANISMS OF ACTION OF NE3107, XPRO, SIMUFILAM AND COYA 301/302

COYA THERAPEUTICS

bioVie

Athira PHARMA

INmuneBio INNATE IMMUNITY

CASSAVA sciences

By: Carl Kestens

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

1. Introduction

1.1. The traditional approach for the treatment of Alzheimer's disease

1.1.1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that causes deterioration of memory, language and thinking, causing patients to eventually lose the ability to perform social and functional activities every day. In general, the average life expectancy for patients after being diagnosed with AD-related dementia is four to eight years.

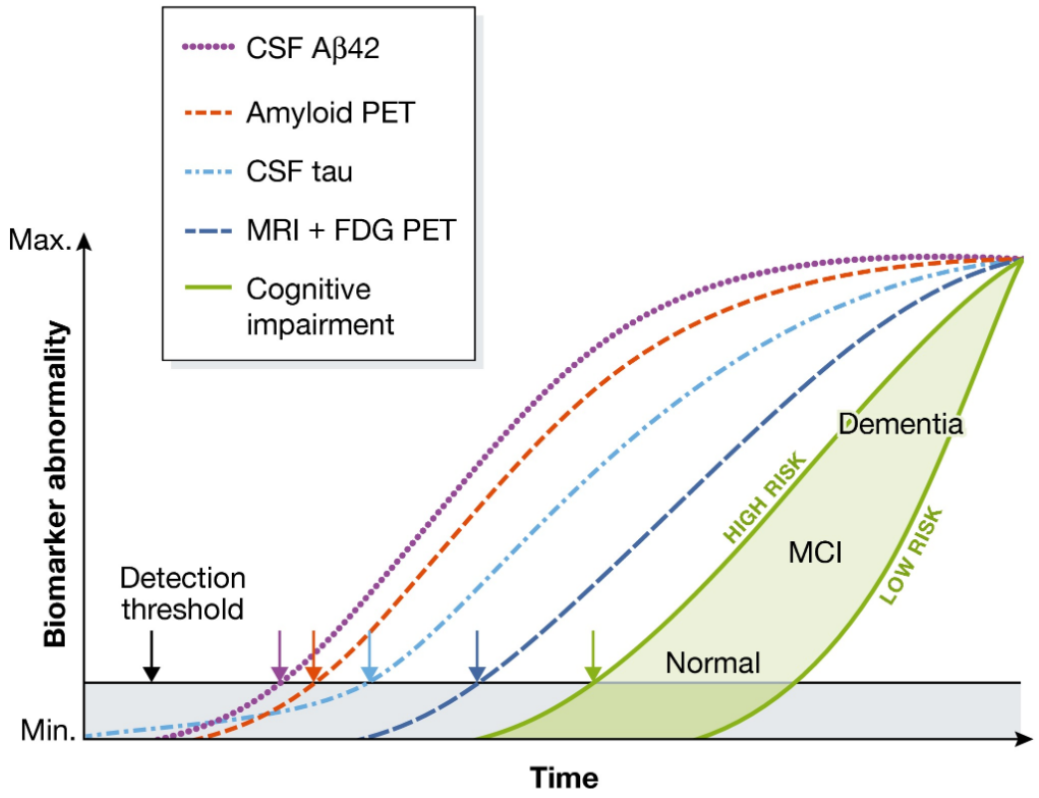
Alzheimer's disease accounts for about 62% of all cases of dementia. AD is the sixth leading cause of death in the United States and is estimated to affect 6.2 million Americans age 65 and older. The global Alzheimer's treatment market is rapidly expanding and is expected to reach $13.7 billion in 2030.

When Alzheimer's disease was first described, four main pathological hallmarks were mentioned: amyloid-β (Aβ) plaques, neurofibrillary tangles, astrogliosis[5], and neuronal loss. The most well-known and most visible of these hallmarks are Aβ plaques and neurofibrillary tangles, i.e. extracellular deposits of Aβ referred to as amyloid plaques and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. From there, several theories about the possible causes of and potential treatments for Alzheimer's disease have been developed. The most well-known theory is the amyloid cascade hypothesis, on the basis of which anti-amyloid antibody therapies have been developed to treat Alzheimer's. Neuroinflammation is now considered an additional hallmark of Alzheimer's disease, although it is actually closely related to astrogliosis and microgliosis.

1.1.2. The early onset of neurodegenerative diseases

Neurodegeneration in most or possibly all neurodegenerative diseases begins years before the onset of symptoms. For example, in Alzheimer's, amyloid aggregation begins earlier than the spread of neurofibrillary tau tangles.

[5] Astrogliosis is characterized by a change in the behavior of astrocytes, immune cells which are also the most numerous cells in the brain. Astrocytes interact with microglia as the resident macrophages of the brain. Both are therapeutic targets in AD.



Source: D. Selkoe et al., The amyloid hypothesis of Alzheimer's disease at 25 years, Molecular Medicine 8(6), March 2016

The same holds true for other neurodegenerative diseases.

There is a need for early detection through the use of the appropriate biomarkers.[6]

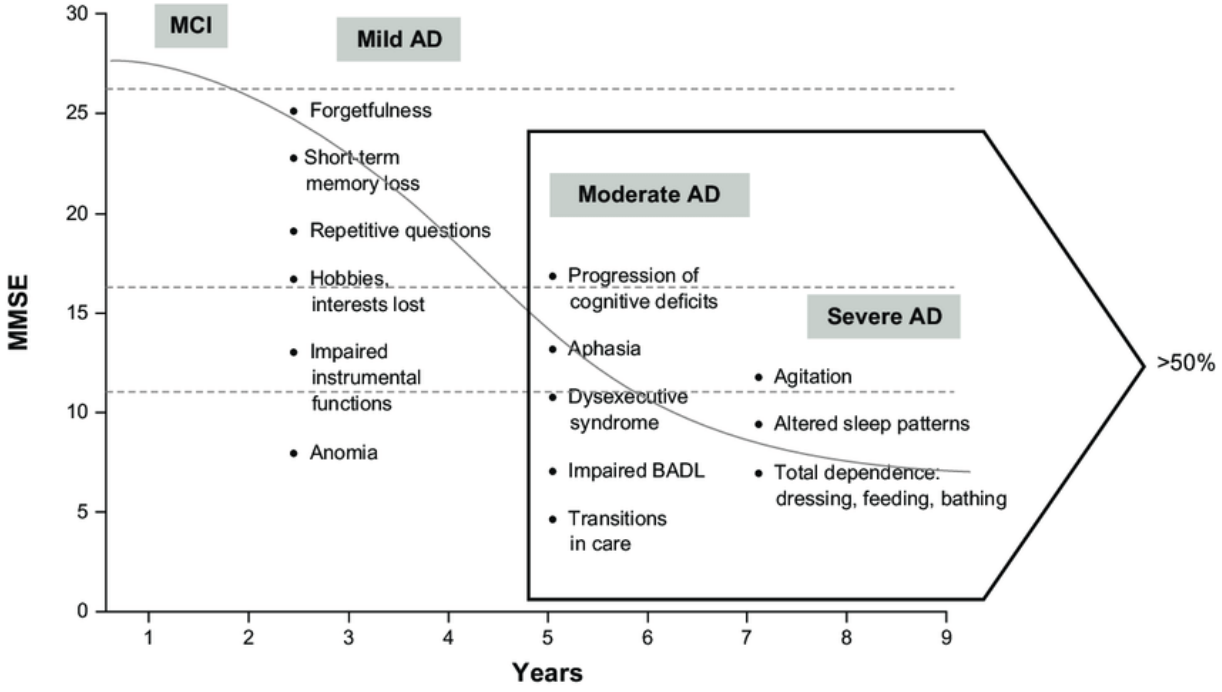
1.1.3. Historical trial failures

The historical failure rate of clinical trials in AD is remarkably high. The list of failed trials is enormous and shows that AD trials have been primarily focused on the reduction of amyloid pathology. Several reasons could be the cause of those failures, including a treatment that intervenes too late in the progression of the disease. Alzheimer's disease is categorized in four stages: the pre-clinical stage, mild AD, moderate AD, and severe or late-stage AD. The first stage often goes unnoticed at first, likely beginning 10 to 15 years before symptom onset. Mild AD is characterized by loss of daily function and memory. Moderate AD is a further stage of progression characterized by difficulties in reading, writing and speaking. In severe AD, patients no longer recognize their relatives.

Those four stages correlate with points on cognitive scales, such as the Mini-Mental State Exam, or MMSE. An MMSE score of 21-26 indicates mild AD, a score of 10-20 indicates moderate AD, and a score of less than 10 indicates severe AD.

Recent successes have been reported in mild cognitive impairment and mild Alzheimer's disease, both of which are earlier stages of disease compared to moderate and severe Alzheimer's disease,

[6] Cfr. infra.



Source: M. Farlow et al., Language impairment in Alzheimer's disease and benefits of acetylcholinesterase inhibitors, Clinical Interventions in Aging, 2013, 1007-14.

Remarkably, of the more recently approved treatments, either on an accelerated or traditional basis, none has been approved for moderate or severe Alzheimer's disease.

Other potential reasons for trial failures include:

- Amyloid has often been used as a primary biomarker of efficacy, although other biomarkers may have been more useful.
- Drug dosage levels for optimal efficacy may not have been sufficiently tested, and Phase 2 trials may have needed more subgroup analysis before designing the pivotal Phase 3 trial.
- AD is a multifactorial disease with much overlap with other neurodegenerative diseases. An inflammatory subgroup, and possibly several others, has not clearly been separated from other subgroups in clinical trials.
- The clinical rating scales used are often not very good at detecting minor changes and may suffer from floor effects in patients with advanced AD.
- Biomarkers were often not chosen as part of the inclusion criteria.
- Finally, due to late diagnosis, some patients entering trials may have reached a disease stage where only a limited treatment effect can still be noted.

1.1.4. Traditional treatments: acetylcholinesterase inhibitors

For the past several years, only symptomatic treatments have been available for Alzheimer's disease, namely acetylcholinesterase inhibitors. These drugs increase the level of acetylcholine in the brain as the acetylcholine-producing brain cells in Alzheimer's patients are damaged or destroyed. Acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine are symptomatic treatments and do not affect disease progression.

1.1.5. Latest developments: provisional/final approval of anti-amyloid antibodies

In 2014, it was reported that Alzheimer's drugs have a 99.6% clinical-failure rate. Before the highly contested accelerated approval of Aduhelm in 2021, no drug had been approved for Alzheimer's disease for 18 years.

After decades of failures, Eisai/Biogen and Eli Lilly announced Phase 3 trial results for their treatment candidates for Alzheimer's disease, reporting 27% and 35% slowing of cognitive decline, respectively. Aduhelm and Leqembi have both been approved on an accelerated basis, respectively, in 2021 and 2022. Aduhelm's provisional approval has not been a commercial success.

However, analysts at GlobalData Healthcare forecast sales of $12.9 billion for Leqembi through 2028. Leqembi will receive an annual list price of $26,500. Centers for Medicare and Medicaid Services (CMS) stated they would intervene in the case of final approval, leading to an expected ~$2.7B spend annually on Leqembi, possibly making it Medicare's single highest drug spend. As with other anti-amyloid antibodies, patients will need to get intravenous infusions twice weekly and may experience brain swelling and bleeding.

Eli Lilly may apply for accelerated approval in the first half of 2023, and donanemab may become the third anti-amyloid antibody in the U.S.

Some other treatments focusing on the reduction of amyloid are being developed, but most of those have not progressed very far yet. Of note here are companies such as Alzheon (private – Phase 3), Acumen Pharmaceuticals (Phase 1) and Prothena Corporation (Phase 1).

As mentioned earlier, Aduhelm, Leqembi and donanemab are anti-amyloid antibodies. The pathophysiological changes and clinical manifestations of AD are progressive and permanent. However, Aβ accumulation may begin 20 years or more before symptoms appear. Recent successes in patients with mild cognitive impairment and mild Alzheimer's disease, which are the earlier stages of the disease, have shown that anti-amyloid antibodies may be able to reduce cognitive decline in patients with mild cognitive impairment or mild Alzheimer's disease to about 40% of the ongoing decline at best, with potentially serious and, in some cases, life-threatening side effects.

1.2. What's ahead: novel approaches

1.2.1. Introduction: the future beyond anti-amyloid

With no additional Phase 3 trials of anti-amyloid antibodies in the near future, the field may turn elsewhere to find different and hopefully better solutions for the treatment of AD.

Cassava Sciences, BioVie, INmune Bio and Coya Therapeutics, the objects of the present research note, are biotech companies involved in the treatment of Alzheimer's disease. They will be discussed in that order, as a function of their market value at the time of writing. This order does not reflect the author's conviction on each of these stocks in that order.

From January 2021 through 2023, these four companies have shown remarkably promising results in their pursuit to treat Alzheimer's disease. Their respective results suggest that cognition can, at least for a certain period of time and in certain patients diagnosed with Alzheimer's disease, be improved

or at least stabilized. These are not the only companies focused on neuroinflammation as a primary culprit in neurodegenerative diseases, and Alzheimer's more specifically. Others such as Athira

Pharma and NervGen could be covered as well, but their reporting so far on cognition is either less compelling or not yet available. For that reason, this research note does not include coverage of these companies.

1.2.2. Apparent disconnect between scientific developments and investments

There appears to be a disconnect between scientific developments on the one hand and the knowledge base readily available to investors in neurodegenerative diseases on the other hand. In-depth analyst reports that offer a comprehensive overview of current developments and the potential of novel treatments for neurodegenerative diseases aiming to reduce inflammation and metabolic dysregulation are scarce.

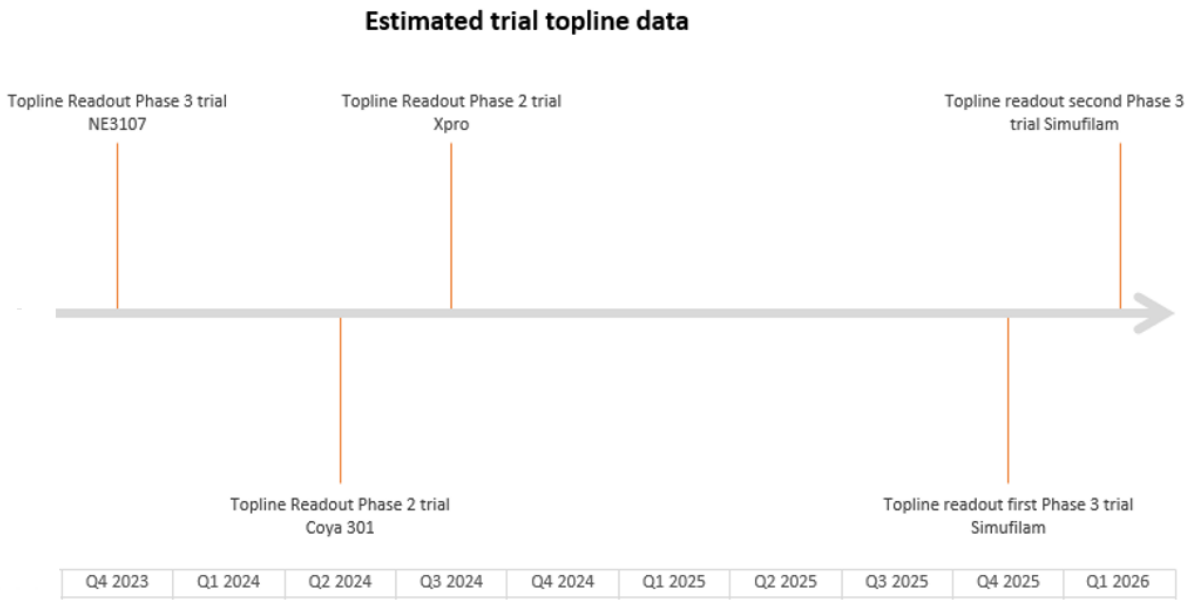
The investment field seems to be stuck on amyloid-related therapies. As a result, the focus of investors appears to remain mostly on novel developments of anti-amyloid therapies, which can be exemplified by the near 60% rise in shares of Acumen Pharmaceuticals after the company presented Phase 1 data for its anti-amyloid oligomer antibody, essentially focusing on amyloid plaque reduction and incidence of ARIA-E. Meanwhile, other companies with clinical trials in later stages that reported the same day saw little to no effect on their share prices.

Nonetheless, the treatment space for Alzheimer's disease and other neurodegenerative diseases is rapidly progressing.

- BioVie has reported favorable biomarker and cognitive data from an open-label Phase 2 study in Alzheimer's disease and a placebo-controlled Parkinson's study in 2022. It is slated to report topline Phase 3 results in October 2023.
- INmune Bio should report topline data from a placebo-controlled Phase 2 study in 2024. In the meantime, some of these companies may communicate further clinical results in AD[7] or possibly other neurodegenerative diseases[8].
- Throughout the first half of 2021, Cassava Sciences reported biomarkers and cognitive data from an open-label Phase 2 study that received broader attention, and in Q3 2023, it reported results from a randomized, placebo-controlled "cognition maintenance study" that followed patients after having been on simufilam for a year.
- Coya Therapeutics has reported stabilization of disease in both ALS and Alzheimer's from small, open-label studies with two different treatment candidates.

Below is an estimate of the essential topline readouts of different placebo-controlled trials for these companies, with a focus on trials in Alzheimer's disease only. This does not include other potential placebo-controlled trials that may be started by any of these companies.

[7] E.g. INmune Bio may report data from an open-label extension study of the placebo-controlled Phase 2 trial, which has been partially delayed by a US-related clinical hold.
[8] The latter seems unlikely but not excluded for Cassava Sciences in light of the rationale below and the allusion to a possible broadening to other neurodegenerative diseases of its CEO in the past.



Of note, the Phase 2 trial of Coya 301 is an academic trial, which is to provide guidance to Coya.

1.2.3 Potential similarities between reported effect on cognition and mechanism of action of respective drug candidates

Results reported so far by BioVie, INmune Bio, Cassava Sciences and Coya Therapeutics indicate that their respective drug candidates may outperform the current symptomatic standard-of-care treatments or acetylcholinesterase inhibitors and/or the current anti-amyloid antibody therapies.

Similarities may exist between the mechanisms of action of these companies' drug candidates. All four have, at least in part, an approach that focuses on reducing inflammation and restoring metabolic dysregulation. Similar pathways seem to be used by the respective drug candidates. These similarities may co-validate the results from these companies.

This overview aims to identify similarities in the mechanisms of action of these companies' respective drug candidates. Such an understanding and comparison may allow for better R&D, treatment development and support for the scientific, medical and investing world.

1.2.4. Investor potential

Positive reporting from placebo-controlled trials in Alzheimer's generally coincides with substantial market-value gains in the concerned (big pharma) companies and substantial market value gains for related companies. Eisai projected Leqembi sales of $7 billion by 2030. At the time of writing, the respective market caps of the companies which are the focus of this report and their respective trial stages for AD are:

Company	Market cap	Trial stage
Cassava Sciences	$874 million	3
BioVie	$125 million	3
INmune Bio	$145 million	2
Coya Therapeutics	$47 million	/ *[9] (Phase 2 ALS to start soon, academic Phase 2 in AD ongoing).

Assuming, in case of success, the market-value gains for each of these companies would be between $5 billion and $10 billion, which appears reasonable taking into account Cassava Sciences' historical market cap of almost $5 billion after the reporting of Phase 2 open-label results. Thus, the potential gain related to Alzheimer's disease alone may be immense, (e.g. between ~6x and ~250x, depending on the company and a respective $5 billion to $10 billion market cap).

The current research note assesses the state of play of Alzheimer's treatments, including the mechanism of action of some more novel treatment candidates. These treatments are different, and some of the noted similarities may be incorrect. This research note does not aim to be exhaustive, nor does it address which companies the author considers to have higher chances of success. **Again, the order of appearance of the companies mentioned in this research note does not represent the author's conviction on any of these but is based on similarities seen in the respective mechanisms of action.**

One could argue that:

- BioVie is best-placed in terms of timing[10];
- INmune Bio has been most de-risked with regards to preclinical trials and extensive data from its Phase 1 trial[11];
- Coya Therapeutics has the most investor potential with progress most imminent in ALS[12];
- Cassava Sciences could be closest to traditional approval in Alzheimer's with two large Phase 3 trials ongoing.[13]

[9] Coya has reported data from two open-label studies and will report on one further open-label study ongoing in AD. It plans to immediately move into a Phase 2 study in ALS, and may do the same for AD after having reported data from the above-mentioned ongoing open-label study. This means the current trial stage may misrepresent the company's evolution.
[10] BioVie has ambitions for accelerated approval on the basis of its ongoing Phase 3 trial, in case of successful reporting. In principle, two well-controlled successful trials are necessary for traditional approval.
[11] INmune Bio's trials are, however, facing a clinical hold, only related to the US territory.
[12] The focus here seems to be less on Alzheimer's disease.
[13] In principle, two well-controlled successful trials are necessary for traditional approval. Of note, the author considers that Cassava Sciences' Phase 3 trials incorporate a serious risk, as the (calculated) results in moderate patients from its CMS trial seem to indicate that moderate patients performed worse than placebo over the course of 12 to 18 months of treatment.

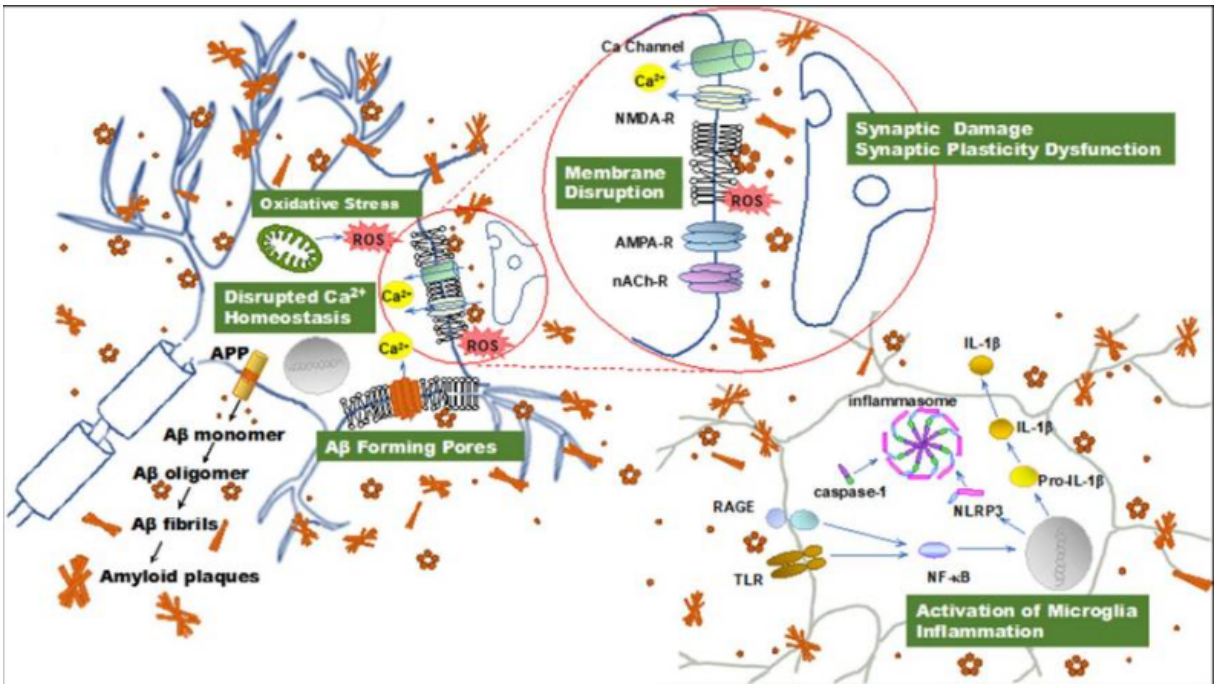
2. Cumulative stressors: amyloid, tau, inflammation and metabolic dysregulation are implicated in Alzheimer's disease

2.1. Introduction

Both amyloid aggregates and hyperphosphorylated tau tangles are the traditional hallmarks of Alzheimer's disease. Amyloid aggregates, the target of the currently approved standard of care such as Aduhelm and Leqembi, are located outside of the cell. Hyperphosphorylated tau tangles are located inside the cell. Inflammation is a more novel hallmark of Alzheimer's disease.

2.2. Amyloid

Amyloid is a general denominator for proteins made by the body. Amyloid-beta is a protein fragment of the APP-protein. In Alzheimer's disease, aggregates of this amyloid-beta are seen in abundance and in different forms, i.e., oligomers, protofibrils and fibrils, with protofibrils potentially being the most harmful.



Source: M. Tsuji et al., Protofibrils of Amyloid-β are Important Targets of a Disease-Modifying Approach for Alzheimer's Disease, Int J Mol Sci. 2020 Feb; 21(3): 952.

It is unclear whether amyloid aggregation into amyloid plaques as such serves a harmful or protective function and/or whether some, but not all, amyloid aggregates are toxic. Alternative theories to the traditional theory suggest that Alzheimer's disease may be the result of an imbalance between the production and clearance of amyloid-beta, with microglia as the main immune cells responsible for clearance of amyloid-beta in the brain, which themselves change to a proinflammatory phenotype and seemingly create an inflammatory loop with amyloid-beta. This makes sense, in light of the fact that amyloid plaques as a traditional hallmark may create a distinction in a disease that should perhaps never have been made. The goal would then be to reestablish that balance to restore homeostasis.

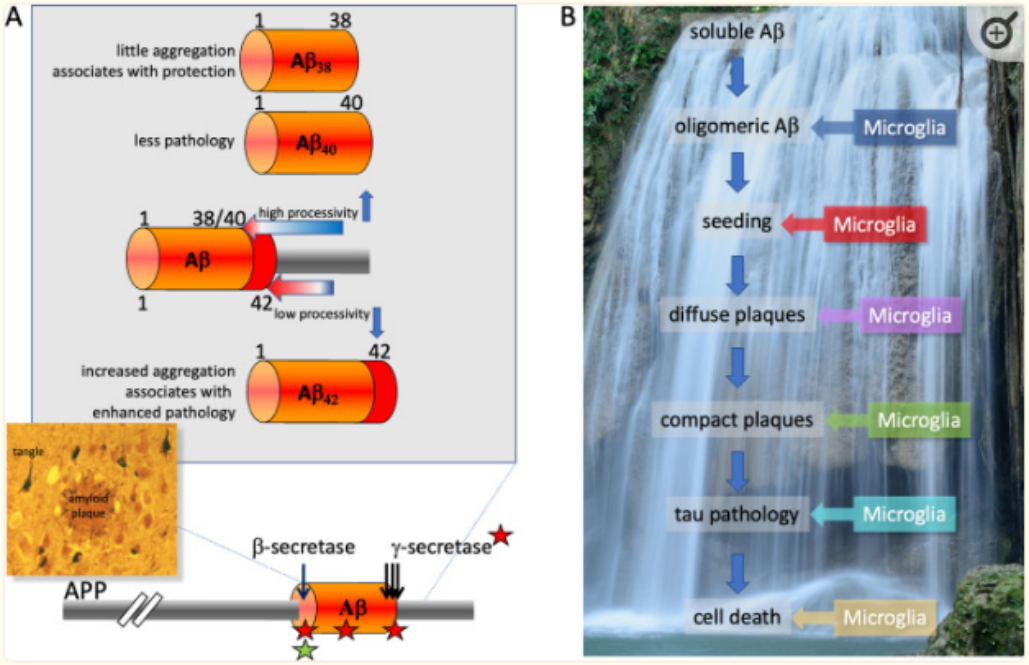


Fig 1 Open in a separate window

Aβ can trigger AD.

(**A**) Proteolytic processing of APP by β-secretase and γ-secretase leads to the generation of Aβ protein. Red asterisks: mutations that cause familial AD; green asterisk: a protective mutation. Insert: typical amyloid plaques and neurofibrillary tangles of AD pathology. (**B**) One way to depict the amyloid cascade. Individual steps in the cascade may evoke distinct microglial responses. Aβ, amyloid β-protein; AD, Alzheimer disease; APP, amyloid precursor protein.

Source: D. Selkoe et al, If amyloid drives Alzheimer disease, why have anti-amyloid therapies not yet slowed cognitive decline?, PLoS Biology, July 2022.

Amyloid aggregation is not specific to Alzheimer's disease. It is also seen in other bodily diseases and in Parkinson's disease. About 30% of older adults also have amyloid aggregation but do not go on to develop Alzheimer's disease. That may suggest removing amyloid plaques may have limited value, which could be seen as confirmed by the massive number of historical failures and all-in-all limited success of anti-amyloid therapies.

Conversely, although Alzheimer's is the most common form of dementia, several other forms of dementia exist that do not involve amyloid aggregates as the typical hallmark. Frontotemporal dementia, for example, usually does not coincide with the formation of amyloid plaques, but it does often coincide with an abnormal buildup of tau. Even in Alzheimer's disease, about 25% of patients are said not to have appreciable buildup of amyloid plaques in the brain.

Recent developments may indicate that amyloid – or a certain type of amyloid aggregates – may act similarly to a pro-inflammatory cytokine, serving as an early responder cytokine and immunopeptide in concert with other pro-inflammatory mediators. This could explain why patients with two copies of the APOE4 gene, which carries the highest genetic risk for Alzheimer's and generally translates into fast disease progression, see reduced efficacy from anti-amyloid antibodies such as Leqembi. The

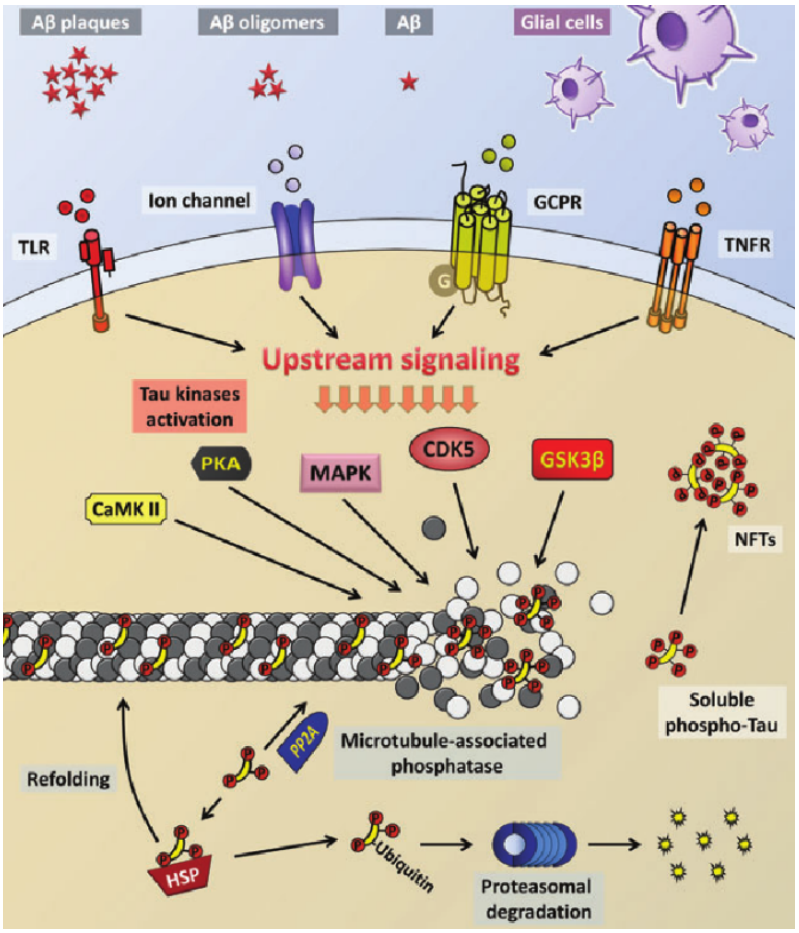
APOE gene comes in three forms, is involved in lipid transport, and influences Alzheimer's disease by exacerbating the Aβ plaque and tau burden, associated inflammation and neurodegeneration. Having two genes increases the risk of getting Alzheimer's disease even more, about eight- to twelvefold. In fact, if amyloid aggregates were truly the sole culprit of Alzheimer's, it wouldn't make sense that their removal in patients with the highest risk for Alzheimer's would be less efficacious than in others.

2.3. Tau

Tau, short for tubulin-associated-unit, proteins are mostly found in neurons. Their essential function is to stabilize microtubules in axons.

In Alzheimer's disease, an abundance of hyperphosphorylated tau is found. Phosphorylation is a common process whereby a phosphate group is attached to a protein. It is a process which often activates many enzymes. When all phosphate binding sites are occupied, one speaks of hyperphosphorylation. When hyperphosphorylated tau is aggregated, one speaks of tau tangles.

Tau tangles are a hallmark of Alzheimer's disease but are not unique to Alzheimer's. Further tauopathies include frontotemporal dementia with Parkinsonism on chromosome-17, Pick's disease, corticobasal degeneration and progressive supranuclear palsy. Tau hyperphosphorylation coincides with loss of function and microtubule disassembly. There is discussion on whether all of these tau aggregates are actually toxic and whether they are not protective in nature as a response to oxidative stress, for example.

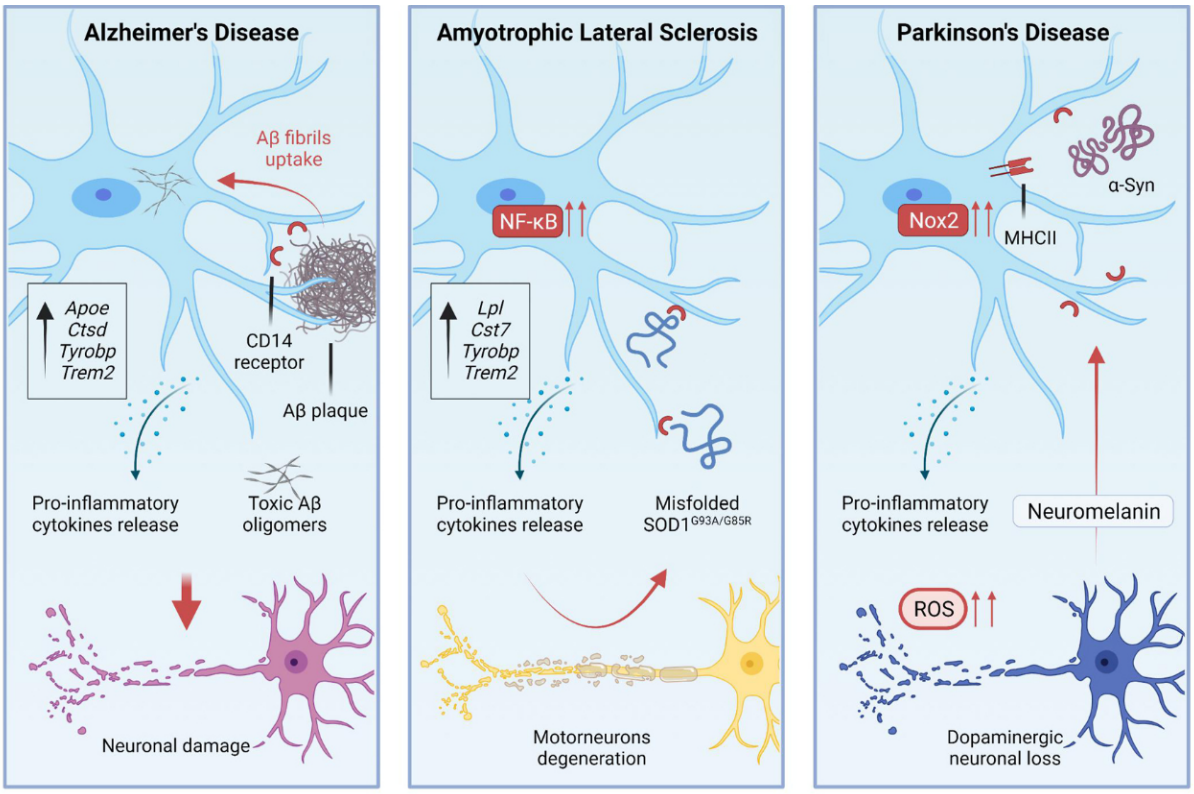


Source: F. Laferia et al., The Role of Tau in Alzheimer's Disease and Related Disorders, CNS Neuroscience & Therapeutics 17(5):514-24, October 2011.

2.4. Inflammation as a more novel hallmark of neurodegenerative diseases

Neuroinflammation is a more novel hallmark that has been established across neurodegenerative diseases.

Neuroinflammation is linked to the pro-inflammatory phenotype of the glia, the brain's immune cells composed mostly of microglia and astrocytes, as seen in neurodegenerative diseases. Glia are non-neuronal immune cells whose functions are to phagocytose and remove cellular debris and act against invaders but also to promote neuro-/gliogenesis, angiogenesis, axonal outgrowth, synaptogenesis and synaptic pruning. In neurodegenerative diseases, they degrade amyloid, but at a given moment in the course of the disease, they polarize toward a pro-inflammatory, non-homeostatic phenotype, which seems to prohibit them from maintaining their essential nurturing and phagocytic functions and may lead to an inflammatory loop.



Source: G. Martino et al, Microglia in Neuroinflammation and Neurodegeneration: From Understanding to Therapy, Front. Neurosci., 24 September 2021.

An emerging role is also attributed to oligodendrocyte precursor cells, the predecessors of oligodendrocytes, the immune cells whose function it is to provide for myelination. Myelin is the substance that allows for insulation of axons, allowing good connectivity between neurons. Oligodendrocytes myelinate axons after axons have connected with their targets. The result of myelination is increased neurotransmission speed and efficacy.

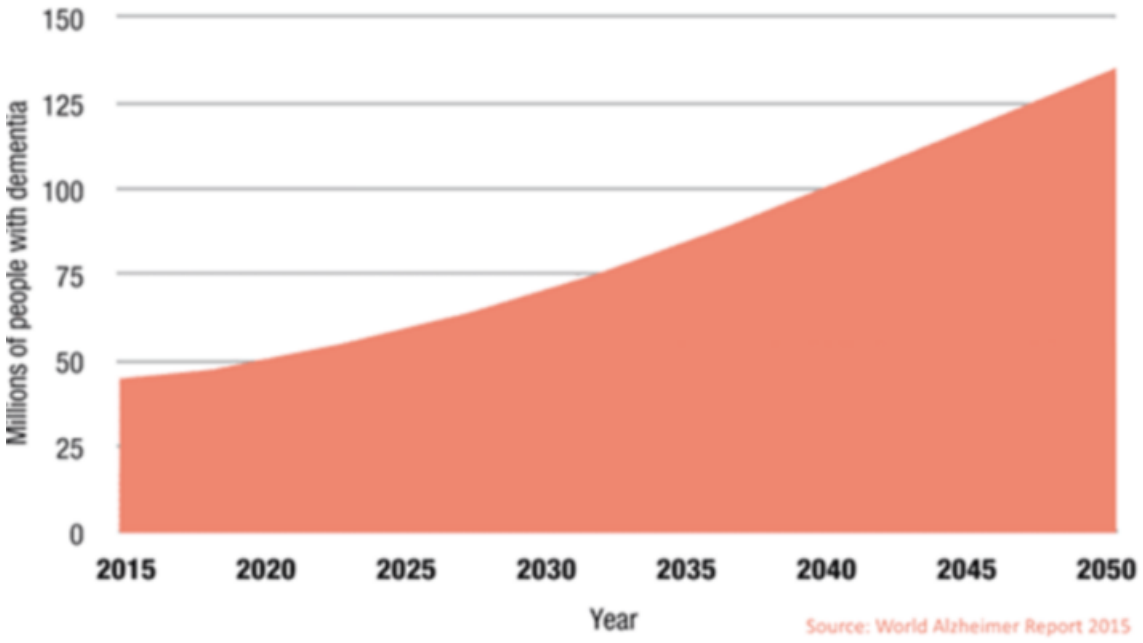
The chronic prohibition of original function, or lack thereof, may be the cause of neurodegeneration, which makes rebalancing polarized microglia a therapeutic target for neurodegenerative diseases. Allowing glia to revert to their homeostatic functions may be essential in preventing neurodegeneration and promoting neuroregeneration.

2.5. The cumulative burden of stressors due to Western lifestyle, metabolic syndrome, toxins and viruses as probable cause of neurodegenerative diseases

2.5.1. Introduction

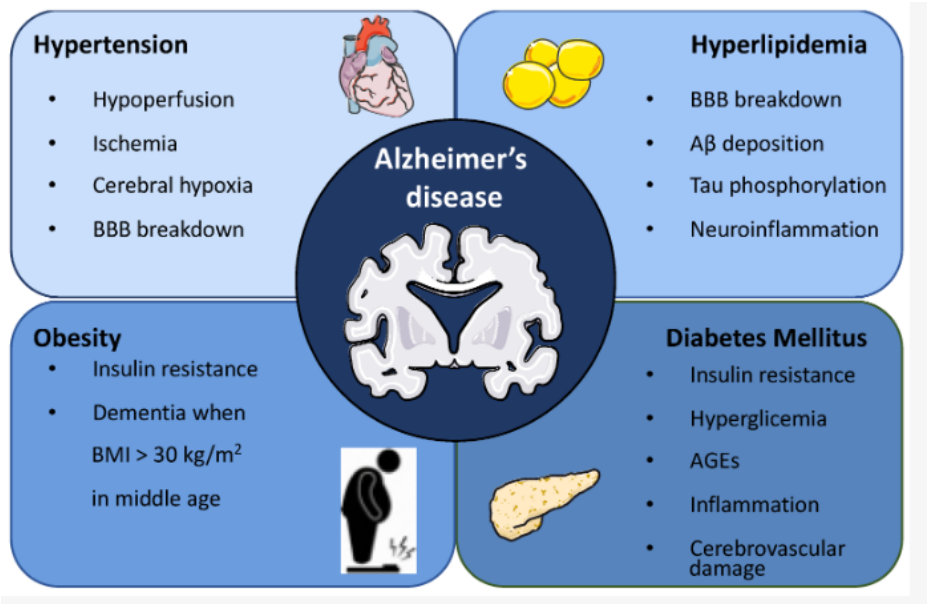
The theory that amyloid deposition directly leads to Alzheimer's dementia has received criticism from all sides over the years. The correlation between the amount of plaque pathology and the degree of clinical dementia is weak to nonexistent. There is a considerable percentage of people with amyloid and tau pathology, the two major hallmarks of Alzheimer's, without dementia, although amyloid- and tau-positive patients may progress to mild cognitive impairment quicker than others. Amyloid pathology seems to be a risk factor for dementia, but nothing more than that. Tau pathology seems to be strikingly more specific than amyloid pathology in predicting cognitive decline. While Alzheimer's

is the most common form of dementia, dementia does not only occur in Alzheimer's patients. It is also seen in a considerable number of Parkinson's patients, referred to as Parkinson's disease dementia. Dementia with Lewy bodies bears remarkable similarities with Parkinson's disease dementia, and frontotemporal dementia is yet another form of dementia. In a large Swedish study identifying similar biomarkers across these dementias, frontotemporal dementia had the highest cerebrospinal fluid levels of amyloid-β1-42 and the lowest levels of total tau and phosphorylated tau. The number of patients diagnosed with dementia is expected to triple by 2050, and in some countries, it is even expected to more than triple.



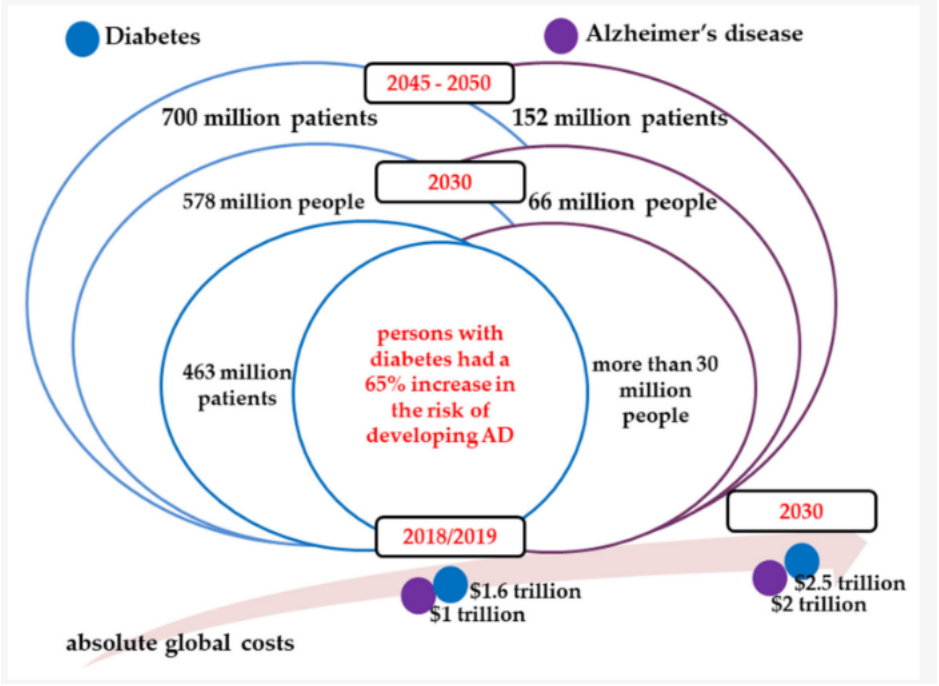
Source: World Alzheimer Report 2015.

When thinking of what causes the disease, it is rather a multitude of triggers that leads to metabolic dysregulation, i.e., coexistence of obesity, hypertension, hyperlipidemia and diabetes, which presents differently in many individuals. Thus, amyloid may rather be a result and accelerator of Alzheimer's disease rather than its initial cause.



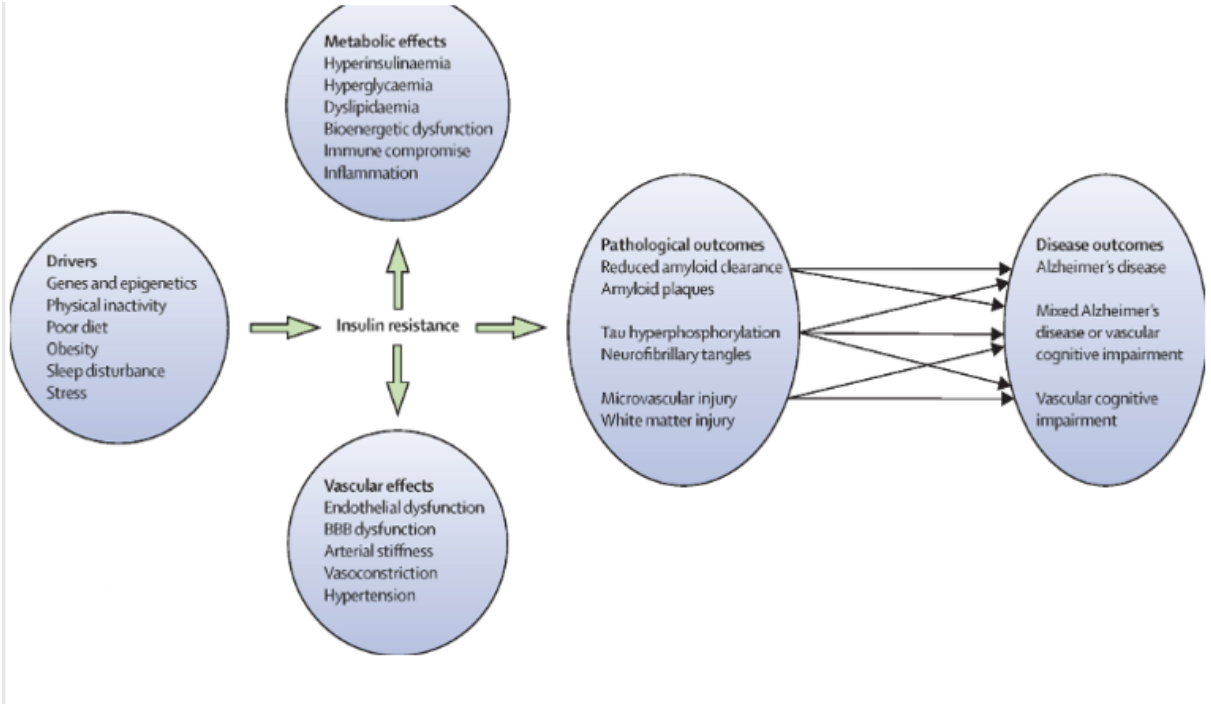
Source: M. Solas et al., Metabolic Syndrome as a Risk Factor for Alzheimer's Disease: A Focus on Insulin Resistance, in International Journal of Molecular Sciences, 2023, 24(5), 4354.

Although aging is still the number one risk factor, 80% of Alzheimer's patients are diabetic and hence insulin-resistant.



Source: D. Bulea et al., Link between Diabetes and Alzheimer's Disease Due to the Shared Amyloid Aggregation and Deposition Involving Both Neurodegenerative Changes and Neurovascular Damages, Journal of Clinical Medicine, 9(6), 1713.

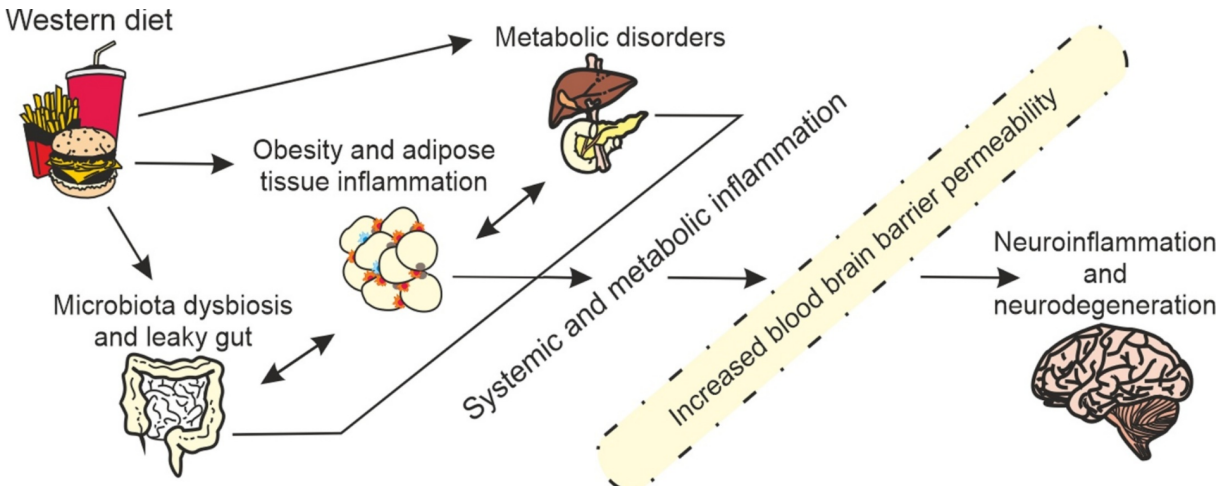
Obesity and brain insulin resistance can, at this point, be considered primary causes, perhaps of more dementias and neurodegenerative indications than Alzheimer's alone.

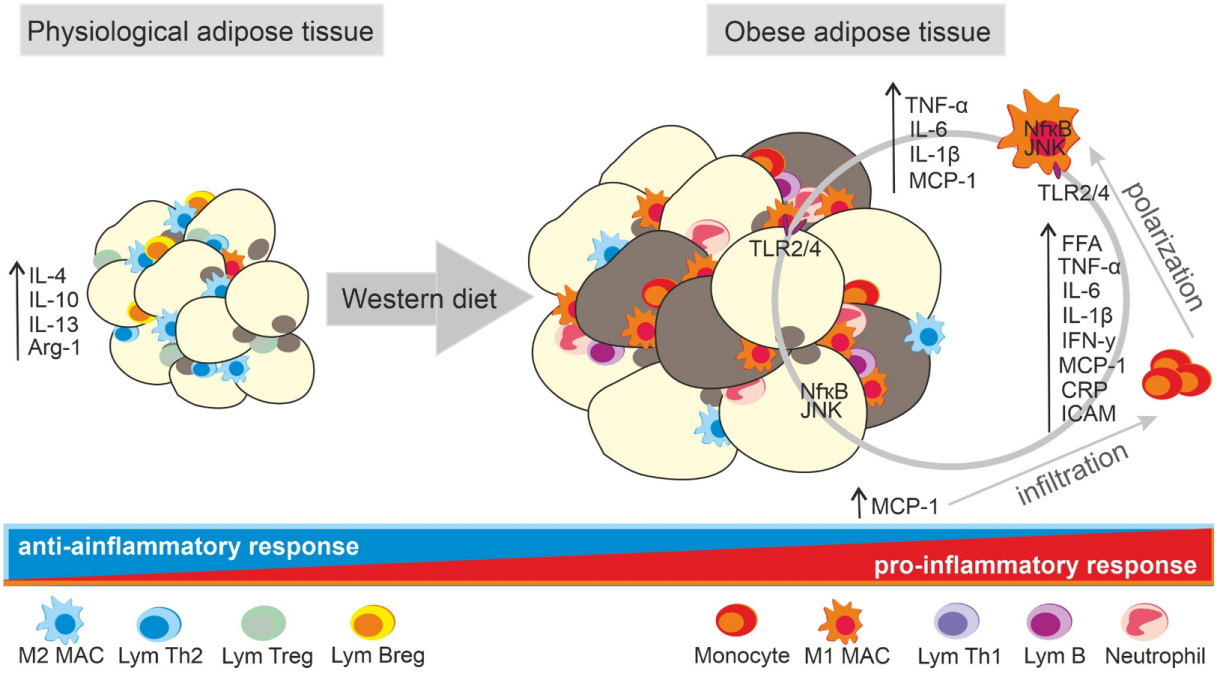


Source: S. Kraft et al., Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches, The Lancet Neurology, Series Diabetes and Brain Health, volume 19, issue 99, p. 758-766, September 2020.

Amyloid deposition is also a common pathological feature in diabetes and Alzheimer's disease.

Obesity and diabetes are diseases of the Western world, and there is good reason to consider the high-fat, high-sugar Western diet and little exercise, which lead to systemic, low-grade chronic (neuro)-inflammation, as directly implicated in the disease.





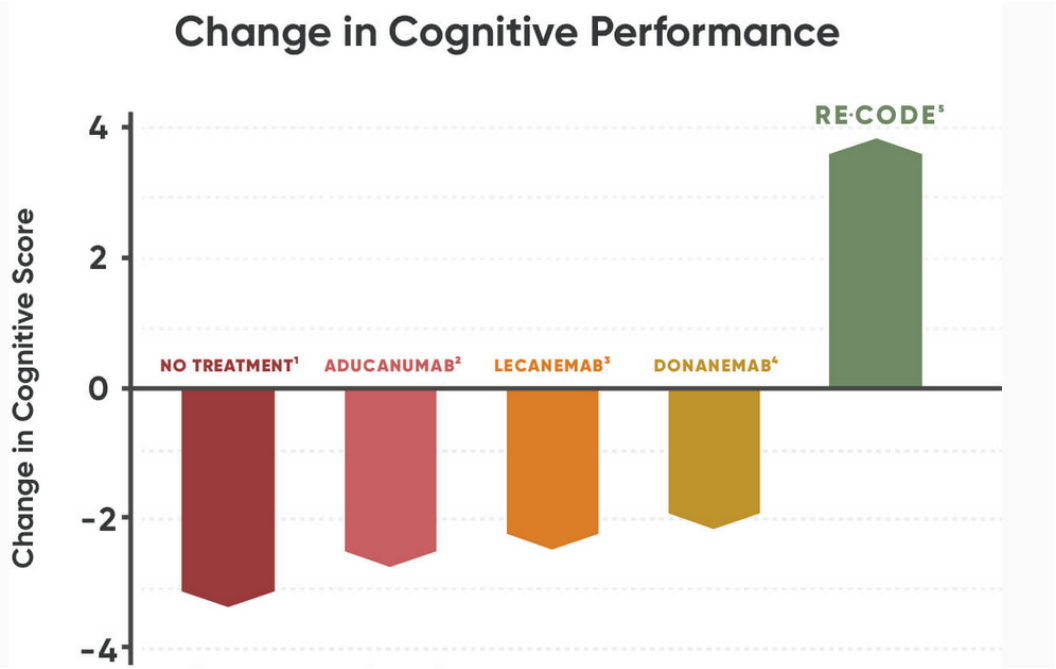
Source: U. Wojda et al., Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration, Ageing Research Reviews, September 2021, 101397.

Exposure to toxins such as pesticides or chronic inflammation through the exposure to viruses common to the globalized world, such as herpes, Epstein-Barr virus, periodontal disease caused by *porphyromonas gingivalis* / *gingipains* or, more recently, COVID-19, also seem to be part of the cumulative burden of stressors, or allostatic load, that may lead an individual to develop a neurodegenerative disease over time.

2.5.2. Early reported success through intense lifestyle and dietary changes

From that perspective, attempts have been made to stabilize or reverse (early) Alzheimer's disease through a number of quite drastic lifestyle changes. The forerunner in that field is Dr. D. Bredesen, who claims that his protocol for identifying Alzheimer's types specific to each patient and subsequent patient-specific treatments has been shown to reverse Alzheimer's in a number of patients. His 2017 book touted his initial results in 100 patients and provided insights on this approach. However, these results were not free from criticism.

In late 2022, the full results of an open-label, proof-of-concept clinical trial entitled ReCode showed that 84% of participants improved their scores on cognitive tests at nine months. Patients had been selected on the basis of inflammation, infection, dysbiosis, insulin resistance, protein glycation, vascular disease, nocturnal hypoxemia, hormone insufficiency or dysregulation, nutrient deficiency, toxin, or toxicant exposure. The basis of the diet was a plant-rich, high-fiber (soluble and insoluble), mildly ketogenic diet, high in leafy greens and other non-starchy vegetables, high in unsaturated fats, and low in glycemic load, with a fasting period of 12–16 hours each night. The diet was to be combined with physical exercise and a sleep regimen to ensure 7-8 hours of sleep. The trial results expressly stated that they had limitations, including the rather moderate improvement and a ceiling effect of some patients on the Montreal Cognitive Assessment Test for Dementia (MoCa) scale.



Source: https://www.apollohealthco.com/alzheimers-reversal/

3. Current treatments and anti-amyloid antibodies

3.1. Treatments approved through 2021

Historical treatments for AD that have been the standard of care for decades include the cholinesterase inhibitors donepezil, rivastigmine and galantamine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine.

However, these drugs offer little benefit to AD patients. It is not known whether these drugs slow down neurodegeneration in AD patients. They are designed to address cholinergic problems in AD by increasing the levels of acetylcholine in the central nervous system (CNS) and the N-methyl-D-aspartate antagonist memantine. Memantine was approved in 2003; it is suggested that it acts by blocking the continuous activation of the excitatory amino acid glutamate receptor by binding to cation channels operated by the N-methyl-D-aspartate (NMDA) receptor.

3.2. The advent of anti-amyloid antibodies

As already explained, the scientific community is working hard to reduce the Aβ burden in AD patients to treat Alzheimer's disease. However, over several years of research and clinical trials, many efforts have failed. Anti-amyloid beta (Aβ) monoclonal antibodies target Aβ aggregates. Aβ accumulation in the brain is considered a major driver of the disease process that precedes the accumulation of tau pathology and neurodegeneration. There are significant differences between anti-Aβ antibodies that interact with different epitope binding and select different forms of Aβ (e.g., monomeric, soluble oligomeric, aggregated forms). In fact, not all amyloid plaques may be bad; some may even be good.
The past 12 months saw the announcement of two statistically significant results coming from Leqembi and donanemab, the amyloid-antibody therapies from Eisai/Biogen and Eli Lilly, respectively. Each of them resulted in multi-billion-dollar marketcap additions.
The results yielded by Leqembi on the CDR-SB scale (Clinical Dementia Rating Scale Sum of Boxes) were a 27% slowing of cognitive decline over the course of 18 months.

Donanemab showed a 35% slowing of cognitive decline on the iADRS (Integrated Alzheimer's Disease Rating Scale) over 18 months.

The amyloid-related imaging abnormalities (ARIA) side effects of anti-amyloid therapies remain an issue, as do the burdensome treatments requiring regular infusions at infusion centers and the cost of therapy.

3.2.1. 2021: Aducanumab / Aduhelm

Aducanumab is an anti-amyloid beta-directed antibody that received accelerated approval for the treatment of Alzheimer's disease, and it is specifically approved on an accelerated basis for patients with mild cognitive impairment or mild dementia.

Accelerated approval is for serious conditions in which the drug is more effective than current treatments and is based on outcomes that reasonably predict a clinical benefit, but not the clinical benefit itself. These predictive outcomes are often markers of disease, but they may also be intermediate clinical endpoints that can be measured before the significant therapeutic outcomes of the final disease.

Aduhelm's approval in 2021 was based on the demonstration of amyloid-beta reduction on positron emission tomography (PET) imaging, a surrogate endpoint determined to have the necessary predictors of clinical outcomes. Reduction of brain Aβ plaques on a PET scan is considered an indicator of clinical outcome in Alzheimer's disease. This conclusion is based on the model showing an association between reduction in brain Aβ plaques and maintenance of clinical activity. It also characterizes brain Aβ plaques as a manifestation of the disease, as seen with aducanumab and other anti-amyloid drugs.

Unfortunately, Aduhelm's commercialization was a complete failure. The drug never received traditional approval, and hence, it could not benefit from CMS reimbursement.

3.2.2. 2022: Lecanemab / Leqembi

Under that same accelerated pathway, lecanemab, sold under the brand name Leqembi, has also been approved based on the reduction of amyloid-beta and a 27% slowing of cognitive decline in patients with mild cognitive impairment or mild Alzheimer's disease. The accelerated approval was based on reductions in the amyloid-plaque burden as measured by PET imaging, which is proposed to be reasonably likely to predict clinical benefit. Traditional approval followed in July 2023.

Lecanemab was found to reduce brain amyloid plaque in a dose- and time-dependent manner. The lecanemab 10 mg/kg biweekly trial arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm.

The below chart shows the difference between patients on the drug and placebo as seen with Leqembi on the primary endpoint using the CDR-SB rating scale.

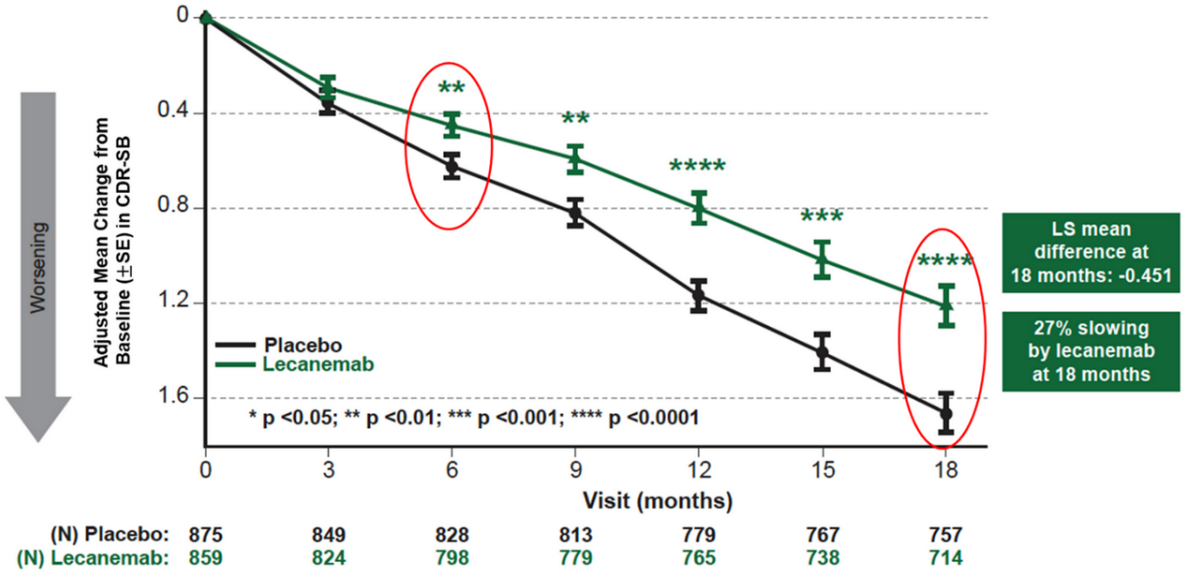
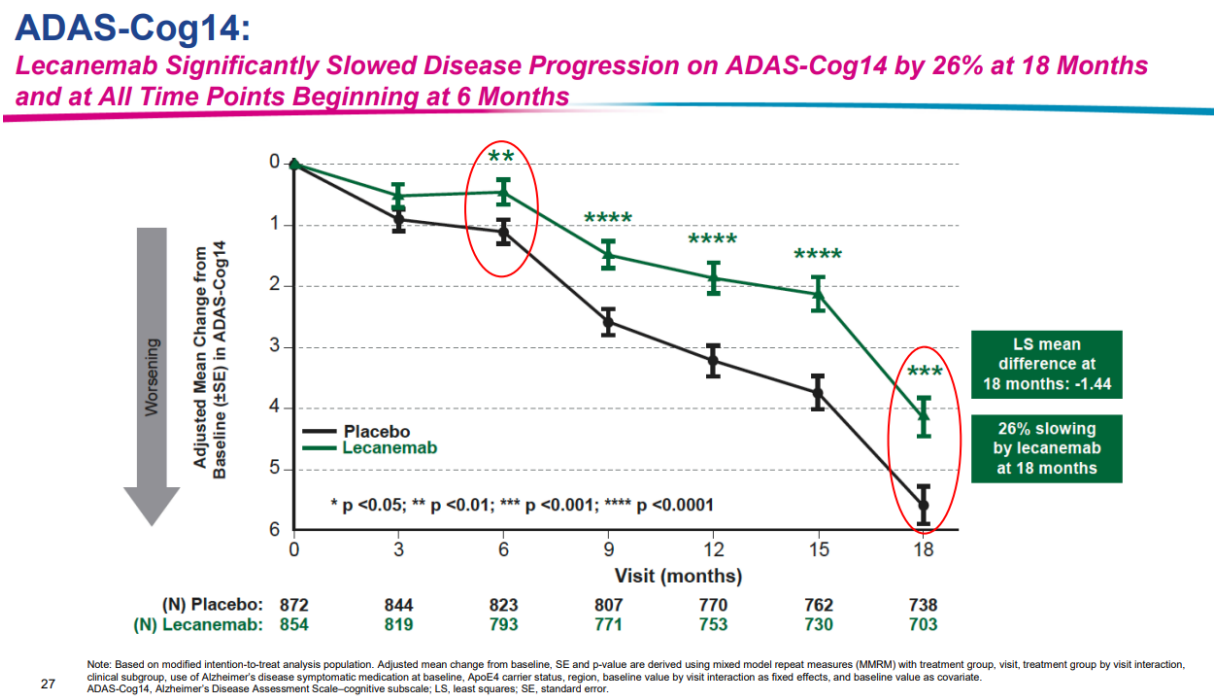


Figure1. CDR-SB as Primary endpoint change (18 months)

Source: Eisai press release, November 29, 2022.

On the Activities for Daily Living scale on the Alzheimer's Disease Cooperative Study (ADCS-ADL), the slowing of cognitive decline was 37%. On the Alzheimer's Disease Composite Score (ADCOMS) rating scale, the slowing of cognitive decline was 24%. On the Alzheimer's Disease Assessment

Scale-Cognitive Subscale (ADAS-Cog14), it was 26%. Interestingly, the slope of decline on that rating scale looks ominous, which could indicate that the patients on the drug may decline faster than those on a placebo between 15 and 18 months of treatment.[14] The other rating scales do not confirm such an effect.



Source: Biogen CTAD 2022 presentation.

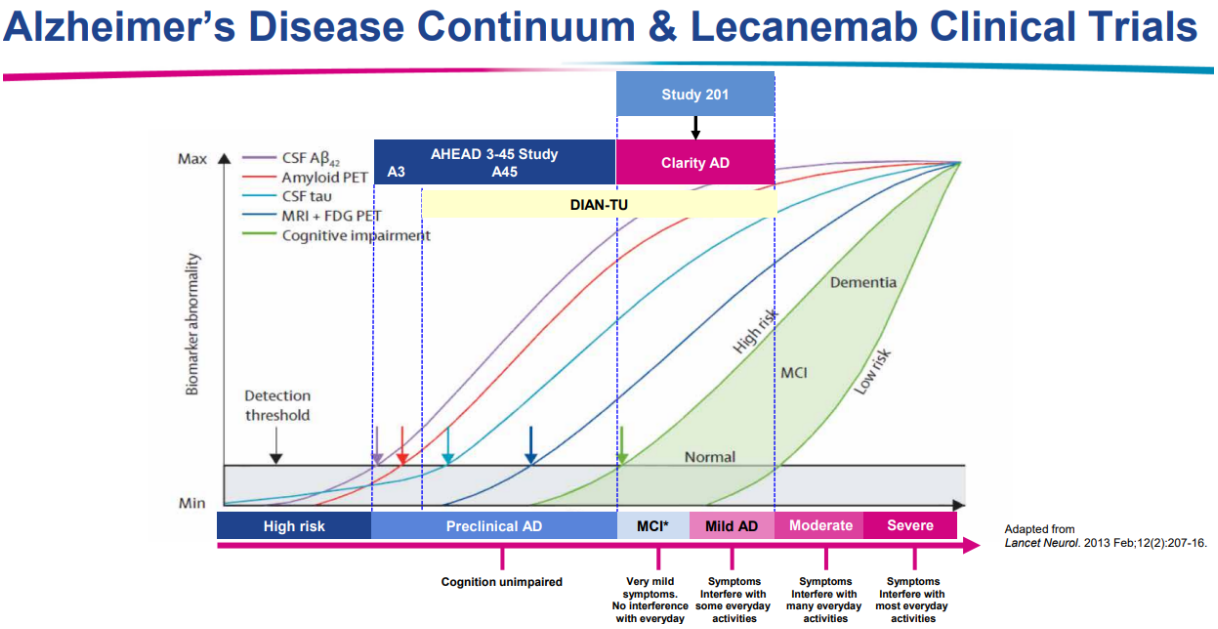
Leqembi received final traditional approval on July 6, 2023 for patients with mild cognitive impairment and mild Alzheimer's disease. Its label will state that efficacy will be reduced for people with two copies of the APOE4 gene.

Lecanemab reduced levels of p-tau181 by about 16% and total tau (4% reduction vs. 15% increase on placebo). Lecanemab reduced levels of GFAP, a marker for astrocyte activation, by 15%, while that marker increased by 10% in the placebo group. Levels of neurogranin, reflecting synapse loss, were reduced by 15%. The Aβ42/40 ratio rose by about 60% in cerebrospinal fluid and 10% in plasma. As to NfL, neurofilament light chain, a well-established biomarker of neurodegeneration, no significant difference was noted, although a trend toward improvement on plasma NfL was found compared to placebo. CSF NfL did not change.

Lecanemab treatment coincides with a notable decline of whole brain volume, decline of lateral ventricular volume, and decline of cortical thickness. Minor improvements in total, left and right hippocampal volume were noted.

[14] There is some skepticism regarding Biogen's results among others related to the slope of decline being similar to that of patients without treatment with Leqembi.

Lecanemab is indicated for the treatment of Alzheimer's disease in patients with mild cognitive impairment or in the mild dementia stage of the disease, the population in which treatment was initiated in clinical trials. There is no approval for moderate-stage Alzheimer's disease.



Source: Biogen [Clarity AD presentation CTAD 2022]

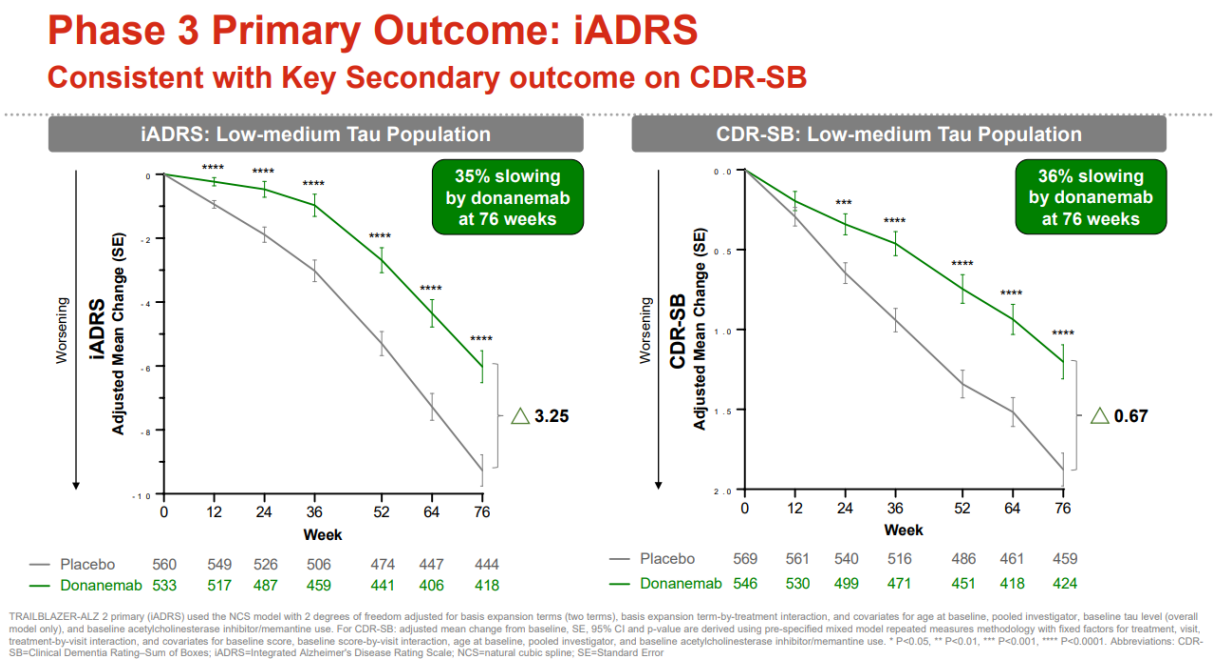
3.2.3. 2023: Donanemab

It is expected that approval of donanemab will follow, based on a similar but slightly higher reduction of cognitive decline. Again, donanemab's [results] are in patients with mild cognitive impairment and mild AD, so it is expected that accelerated or traditional approval will not go beyond those stages of Alzheimer's disease.

Donanemab's results on cognition are [shown below].

Intermediate tau population	MMRM statistical analysis		NCS statistical analysis	
	Relative % slowing	p-value	Relative % slowing	p-value
iADRS	40 %	p<0.0000004	35 %	p<0.000004*
CDR-SB	36 %	p<0.000002*	37 %	p<0.0000005
ADCS-iADL	43 %	p<0.00005	40 %	p<0.0001*
ADAS-Cog13	35 %	p<0.00003	32 %	p<0.00005*

Source: [press release].



Source: Eli Lilly AAIC 2023 presentation – Eli Lilly corporate website.

Additional subpopulation analyses showed study participants with mild cognitive impairment, i.e., at the earliest stage of disease, having greater benefit, with 60% slowing of decline compared to the placebo group. Furthermore, treatment effect continued to increase relative to placebo over the course of the trial, even though many participants completed their course of therapy at six or 12 months, supporting limited-duration dosing.

Additionally, Eli Lilly reported at AAIC 2023 that the treatment effect of donanemab widened over time, even after patients were switched to placebo.

3.2.4. The Alzheimer's pipeline

After Eli Lilly reported its latest results for donanemab, the Alzheimer's Drug Discovery Foundation released a statement underscoring the need to develop additional drugs "*that target other pathways guided by the biology of aging.*" It stressed the need for combination therapies like in other complex diseases of aging. Its co-Founder and chief science officer, Howard Fillit, MD, considered: "*But this is just a start, and we must continue advancing the drug pipeline to develop the next class of drugs centered around the biology of aging to ultimately stop Alzheimer's in its tracks. Like in cancer, the goal is to address the many underlying pathologies of the disease through a precision medicine approach*." The Alzheimer's Drug Discovery Foundation further considered that, based on the biology of aging, there are multiple pathways involved in the onset of Alzheimer's, with the accumulation of misfolded proteins serving as one target in addition to inflammation, metabolic disturbances, vascular dysfunction and more. The robust drug pipeline—where 75% of drugs in clinical development are focused on novel pathways—is primed for this next phase of clinical trials.

The different treatment candidates for Alzheimer's in 2023 are shown below. Not coincidentally, two of these treatment candidates are repurposed anti-diabetes drugs, which makes sense given the connections that have been discovered between Alzheimer's and diabetes.

Some of the disease-modifying treatments have been discussed above; others will be highlighted below[15].

- Semaglutide (Ozempic) is Novo Nordisk's GLP-1 agonist to improve insulin sensitivity and reduce inflammation, with a Phase 3 readout in Alzheimer's[16] expected in September 2025[17].

- Metformin is another insulin sensitizer traditionally used as a diabetes medication.

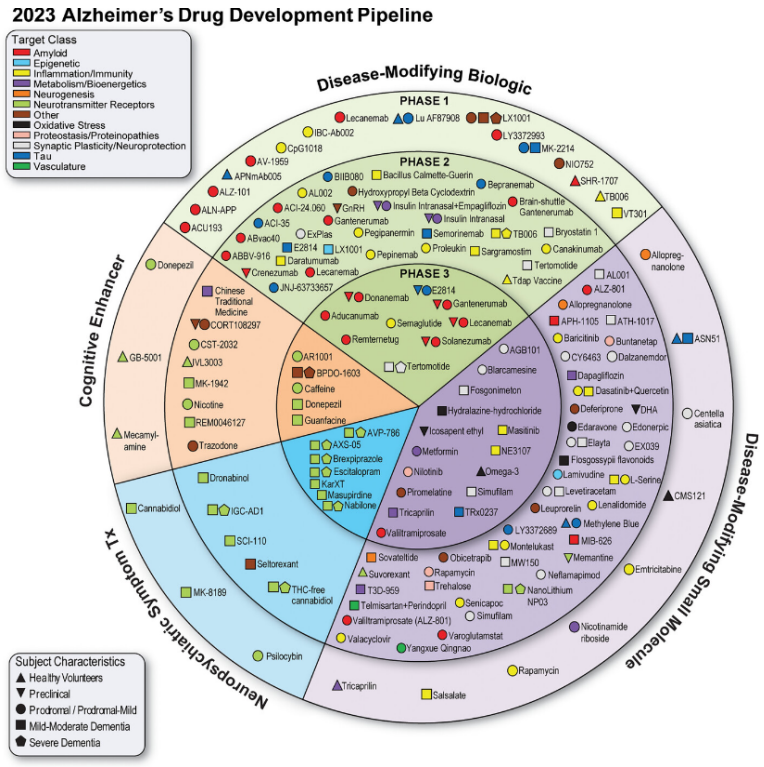
- Solanezumab and gantenerumab, two anti-amyloid antibodies, were reported to fail in 2023.

- Remternetug is another anti-amyloid antibody in trials for Eli Lilly, with a Phase 3 readout expected in March 2024.

- Blarcamesine is Anavex's drug candidate, the results of which were reported in December 2022.

- Fosgonimeton is Athira Pharma's drug candidate.

- Valiltramiprosate is Alzheon's drug candidate, with a Phase 3 readout expected in May 2024.



[15] For an entire list, look here.

[16] Real-world data and post-hoc analyses of three large cardiovascular outcome trials of semaglutide and liraglutide had shown that there was a53% reduction in the risk of developing dementia in people with Type 2 diabetes who took either GLP-1 agonist compared to placebo. Those combined results, together with preclinical results, form thebasis for this Phase 3 trial.

[17] Of note:

- Exenatide, another GLP-1 receptor agonist, had in 2017, in the framework of a Phase 2 study, shown that it may slow the progression of Parkinson's. The results of a Phase 3 study are expected to follow in mid-2024.
- Neuraly's GLP-1 agonist NLY01 was reported to be safe but failed to report statistical significance in Parkinson's disease in March 2023.

Source: J. Cummings et al., Alzheimer's disease drug development pipeline: 2023, Translational Research and Clinical Interventions, 2023, vol. 9, issue 2.

It is also the author's view that, with one anti-amyloid antibody now having been approved and a second one probably to follow, the scientific and investing field has seen the potential of anti-amyloid therapies and may focus on further solutions.

3.2.5. Safety issues

Monoclonal antibodies directed against aggregated forms of beta amyloid, such as lecanemab, can cause mild or moderate infusion-related reactions and amyloid-related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis.
Incidence of infusion-related reactions is about 10% to 20% and includes symptoms such as fever and flu-like symptoms.
Incidence of ARIA in anti-amyloid therapies is about 10% to 15%. Common symptoms are headache, confusion/mental status changes, agitation and visual disturbance.

3.3. Unmet medical needs

3.3.1. The need to act earlier in the development of the disease

Given the early onset of neurodegenerative diseases, there is a need to intervene early in the disease process. Both diagnostic tools and early intervention could allow for better treatments and prevent the disease from developing into later and more devastating stages.

3.3.2. Shortcomings of anti-amyloid antibodies

Apart from their limited efficacy, anti-amyloid antibody treatments come with safety issues, are expensive, and require regular infusions, hospital intake, and lengthy treatments. There is a need for treatments with a better safety profile that are less expensive, allow for oral or subcutaneous dosing[18], and avoid the need for hospital intake and lengthy treatments.
Additionally, anti-amyloid antibodies, or at least Aduhelm and Leqembi, appear to lead to a decline in brain volume. For Leqembi, a decline in cortical thickness was also noted. There may be a need for therapies that lead to a stabilization or increase in brain volume and cortical thickness.

3.3.3. The need for further-reaching / personalized / combination therapies

There is an urgent and unmet medical need for more effective treatments for AD and a particular unmet need for therapies in AD that slow, halt, reverse, prevent or cure the disease with drugs that target its underlying pathophysiology in an effort to fundamentally affect the course of the disease, an important focus of development. This may be either by the use of one drug alone or by way of a combination treatment.
The slope of decline as shown with lecanemab may indicate that the treatment effect will only last for a certain amount of time. Thus, there may be a need to find treatments with longer-lasting efficacy.
There is also a need for further identification of the potential individualized causes of Alzheimer's disease, which would allow personalized and improved treatments.

[18] Eli Lilly touted promising data on a subcutaneous version of donanemab in July 2023.

3.3.4. The need for treatments for moderate and severe Alzheimer's disease

It should be noted that none of the anti-amyloid antibodies have been tested in moderate or severe Alzheimer's disease, which are particularly hard to treat. The moderate and severe stages of AD represent smaller markets and are characterized by faster declines.

Patients with those later stages of disease are not likely to be able to benefit from any approval of anti-amyloid antibodies. Thus, there is also an unmet medical need to provide solutions for patients with these stages of the disease.[19]

[19] BioVie and Cassava Sciences are targeting moderate Alzheimer's disease as well, though data from Cassava Sciences' CMS trial, in which moderate patients on simufilam apparently underperformed the placebo group between 12 and 18 months, according to the author's calculations, may have also led to a lack of statistical significance for the entire trial,which is not encouraging.

4. Novel approaches for the treatment of Alzheimer's disease focusing on inflammation and metabolic dysregulation

4.1. Introduction

For quite some time now, the scientific field has been looking at different approaches, including involvement of cytokines and immune cells, to treat neurodegenerative diseases. These approaches focus on reduction of inflammation and metabolic dysregulation and are mostly but not exclusively[20] developed within biotech companies. Levels and progression of inflammation are regulated by the expression of a variety of messenger molecules referred to as cytokines and chemokines. The most commonly cited pro-inflammatory cytokines are TNF-α, IL-6 and IL-1β.

Glial cells, the brain's immune cells, make up 90% of the cells in the human brain. Microglia and astrocytes, two primary immune cells of the brain, have been implicated in inflammation. The implicated inflammatory pathways are mediated by toll-like receptors on the cell membrane, such as TLR4, and NF-kB inside the cell.

TLR4 has been reported to lead to inflammatory cytokine release. TLR4 is expressed in microglia, astrocytes and oligodendrocytes as immune cells of the CNS, which are in a pro-inflammatory state in Alzheimer's and other neurodegenerative diseases. TLR4 is considered a target for the treatment of AD, whereby TLR4 (and, on a much smaller scale, some other TLRs function as pattern-recognition receptors to induce inflammation. TLR4 specifically recognizes lipopolysaccharide, a major contributor to diabetes and insulin resistance. Stimulation of TLR4 leads to inflammation through a complex cascade of processes involving, among others, IL-1, TNF, NF-kB and the MAPK signaling pathway, which includes ERK, JNK, and p38. TLR4 is expressed more in APOE4-positive individuals. APOE4, a gene responsible for lipid transport, is the highest risk factor for AD. The APOE4 allele is linked to and mediates inflammation and neurodegeneration and promotes formation of amyloid plaques.

NF-kB signaling has been reported to play a critical role in the pathogenesis of AD by being activated through TLR2, TLR4, and CD14 and by reportedly, among others, contributing to tau pathology and APOE promotion through amyloid plaques.

4.2. Potential of NE3107, XPro, simufilam and Coya 301/302 to restore cognitive function

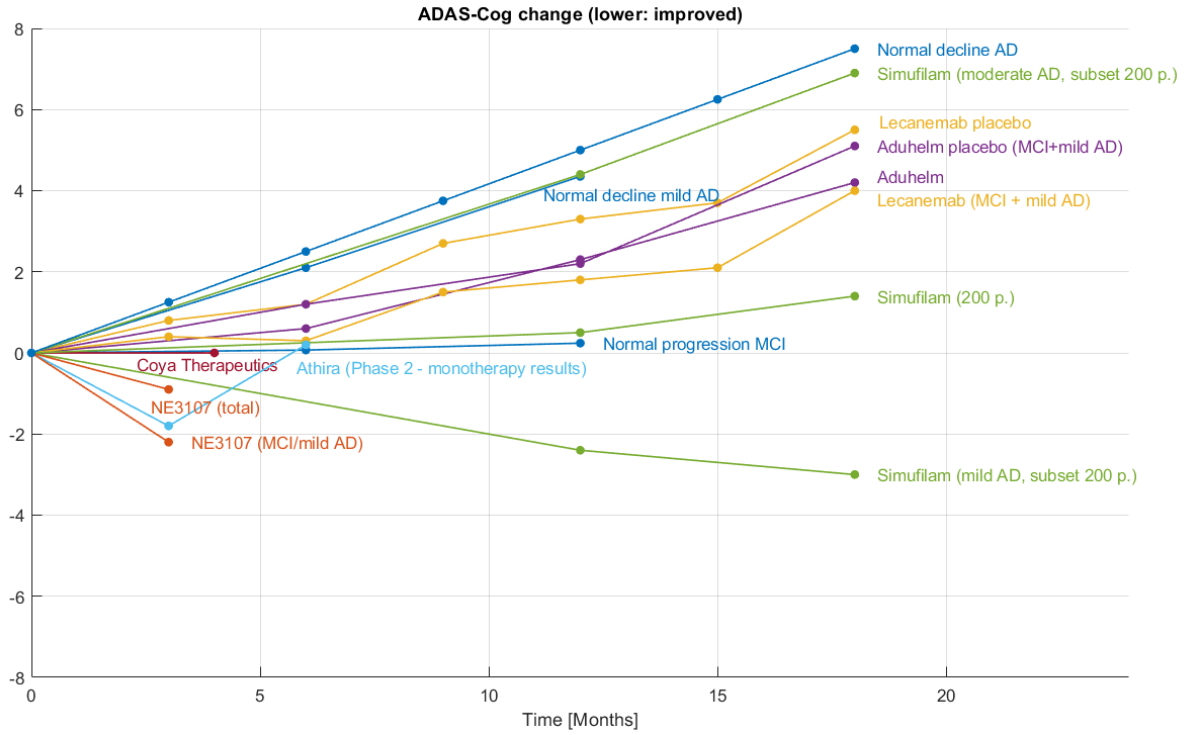
4.2.1. Introduction

The companies reported below may have anti-inflammatory drug candidates that, on the basis of the results reported so far, may yield far better results in the future. So far, most of the reporting has been from open-label studies. Cassava Sciences' placebo-controlled study on patients who took the drug for 12 to 18 months generated mixed results which did not have statistical significance.

[20] In Parkinson's, Roche's randomized study of candesartan for cognitive impairment in Parkinson's disease showed reduction of TLR2 and TLR4 expression *in vitro* and *in vivo*. Inflammation induced by a-synuclein in Parkinson's has been reported to be induced by microglia and monocytes and mediated by TLR2 and TLR4. Candesartan is an angiotensin-II type 1 receptor blocker licensed for hypertension. No statistical effect was seen on cognition.
Roche is also pursuing a Phase 1b trial of selnoflast, an NLRP3 inhibitor focusing on the inflammasome, an interesting target to reduce inflammation. Several other NLRP3 inhibitors in various stages of preclinical development have been bought by big pharma.

If multiple companies report statistically significant success from a well-controlled Phase 2 or Phase 3 trial, the question of which approach may ultimately be the best one will be another issue entirely. The best approach may not necessarily be most successful in terms of revenue. Being the first to market provides an advantage, although other factors may be of importance too.

The results from both BioVie's NE3107 and Cassava Sciences' simufilam on different ADASs-Cog rating scales, where fewer points mean more cognition, underscore that potential. The comparison below aims to combine data from different ADAS-Cog rating scales into one on the basis of available data. The tentative comparative chart of cognitive evolution after treatment is created on the basis of the limited information made available to the public, where lower numbers are better. The results from Cassava Sciences' Cognition Maintenance Study have not yet been included.



Source: own work – lower results are better.

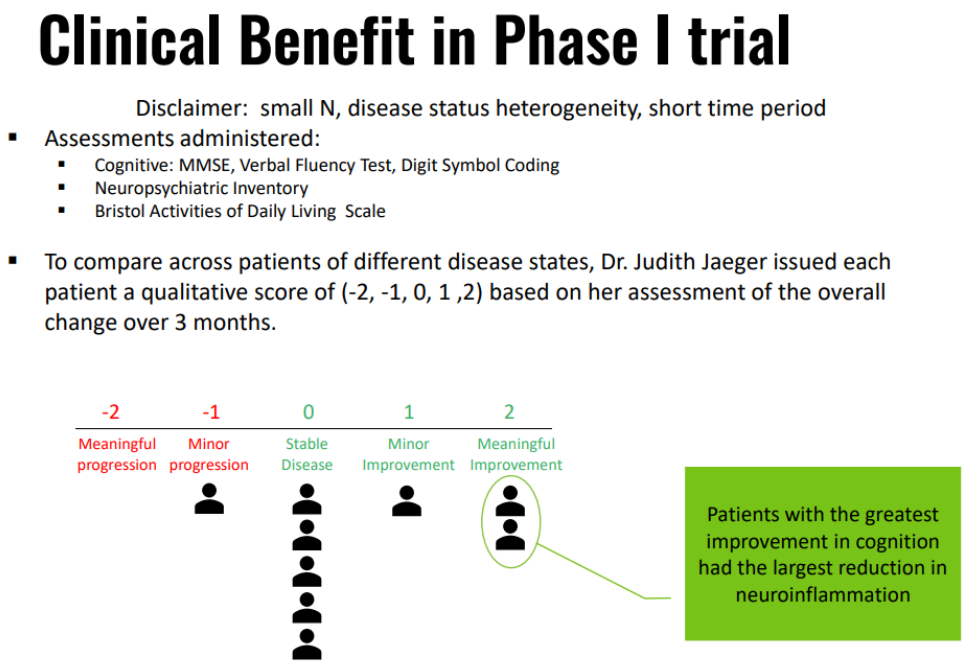
4.3.2. BioVie – NE3107

BioVie reported the following clinical data on cognition from its open-label Phase 2 data over the course of three months, with mild cognitive impairment (MCI)/mild AD being the intent-to-treat population with highest enrollment:

Assessment	All Patients (N=23)	MCI/Mild AD (n=18)
ADAS-Cog12	−0.913	**−2.167***
MMSE	−0.74	−0.39
MoCA	−0.04	0.56
QDRS	−0.54	**−1.56***
CDR	0.04	**−0.11***
ADCOMS	0.0049	**−0.07***

4.3.3. INmune Bio - XPro

Although cognitive testing in its Phase 1 trial in Alzheimer's has already taken place, INmune Bio has not reported cognitive data yet and hence could not be included in the chart above. Its corporate presentation, however, includes indications of positive results from clinical measurements taken from its Phase 1 trial.



Source: INmune Bio corporate presentation, accessed June 2023.

Of note, BioVie and INmune Bio reported correlations between reduced inflammation and cognitive stabilization or improvement.

4.3.4. Cassava Sciences - simufilam

Cassava Sciences reported the following clinical data on cognition from its open-label Phase 2 trial over the course of 12 months, as measured on different rating scales.

Top-line Results – mean scores, baseline to month 12 (*lower is better, except for MMSE*):

ADAS-Cog11 scores changed from 19.1 (±9.2) to 19.6 (±13.3)

MMSE scores changed from 21.5 (±3.6) to 20.2 (±6.4)

NPI10 scores changed from 3.2 (±4.6) to 2.9 (±4.6)

GDS scores changed from 1.8 (±1.8) to 1.4 (±1.9)

These data points are mentioned first, as they concern the initial treatment of patients. Cassava Sciences has subsequently enrolled these patients in a randomized, placebo-controlled manner in a so-called Cognition Maintenance Study for an additional six months. The results of one such study as reported by Cassava Sciences are shown below.

Full Analysis Set	**Drug (N = 78)**	**Placebo (N = 77)**
6-month Change in ADAS-Cog	- 0.9 point decline	- 1.5 point decline

Source: Cassava Sciences press release of July 5, 2023.

Mild Patients	**Drug (N= 40)**	**Placebo (N= 36)**
6-month Change in ADAS-Cog	0.6 point improvement	- 0.6 point decline

Source: Cassava Sciences press release of July 5, 2023.

The study may not have been powered for statistical significance, and it didn't reach statistical significance. However, the overall result is positive, certainly after a year on the drug. The result in mild patients is positive, again knowing that they were on simufilam for a year. Upon randomization, these patients with mild Alzheimer's disease had a baseline mean MMSE score of 24, which is similar to the mean score of patients in the Phase 3 trial for lecanemab (mean: 25). That also means patients with mild disease were on the milder end of the mild AD spectrum (mild Alzheimer's disease: MMSE 21–26, moderate Alzheimer's disease: MMSE 10–20, moderately severe Alzheimer's disease: MMSE 10–14, severe Alzheimer's disease: MMSE less than 10). Insofar as it can be taken as a reference to anti-amyloid antibodies and their modest slowing of cognitive decline, Cassava Sciences' July 5, 2023 press release mentioned that simufilam treatment over six months slowed cognitive decline in mild Alzheimer's disease by more than 200% compared to placebo. The difference with the effect of anti-amyloid antibodies – also tested in mild AD, but also in the prior MCI stage – is noticeable, but the results were not statistically significant, possibly due to the small patient population.

There is a side note. Simufilam appears to have performed much better in the patient population with mild Alzheimer's disease than in the patient population with moderate Alzheimer's disease. No data have been communicated by Cassava Sciences for the moderate patient population, which is not covered by anti-amyloid antibodies. By the author's estimates, the data for the groups with moderate

Alzheimer's disease could be the following (these are estimates). As mentioned below, the author believes this creates a risk for Cassava Sciences' ongoing Phase 3 trials.

Moderate Patients	**Drug (N= 38)**	**Placebo (N= 41)**
6-month Change in ADAS-Cog	- 2.5 point decline	- 2.3 point decline

Source: own work.

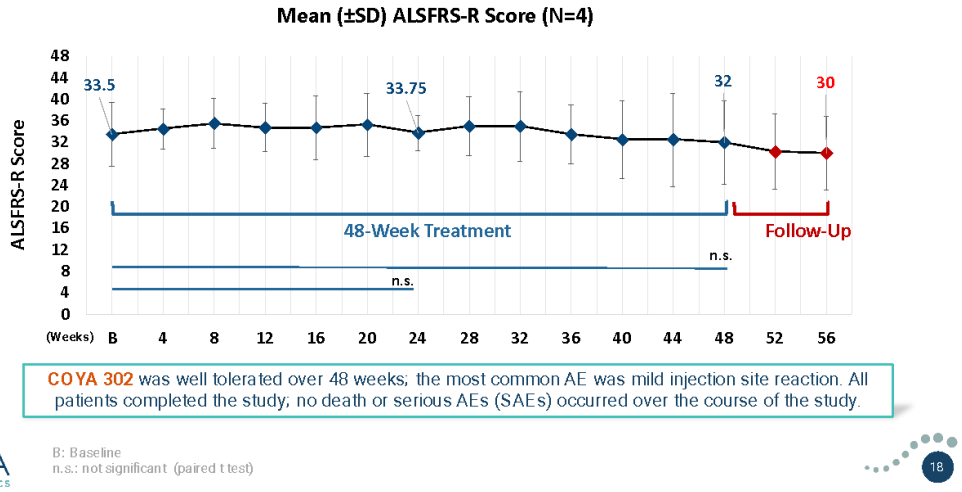
4.3.5 Coya Therapeutics – Coya 301/302

Coya Therapeutics is undertaking a different anti-inflammatory approach that involves directly modulating regulatory T cells, or Tregs. Tregs play a "master regulatory" role in the inflammatory cascade in neurodegenerative diseases by affecting different pathways, including TNF-alpha and other downstream cytokine pathways. As the pathway is being blocked upstream, chances may be higher that the immune system will not find ways to use the other pathways that are being inhibited, resulting in a greater and potentially longer-lasting inhibitory effect.

As part of a plan to develop combination therapies, Coya uses low dose IL-2 as a standard *in-vivo* approach to enhance Treg function and numbers. By administering only low-dose IL-2, Coya has reported stabilization of cognition in Alzheimer's patients in a small open-label study. In eight patients treated over a four-month treatment period, Coya reported a statistically significant improvement in cognitive function as measured on the MMSE rating scale and no cognitive decline as measured on the ADAS-Cog and CDR-SB rating scales. Interestingly and in line with reporting from INmune Bio and BioVie, Coya's treatment not only resulted in a statistically significant reduction of three pro-inflammatory cytokines often considered as major drivers of inflammation, namely, TNF, IL-6 and IL-1β, but it also correlated with a lack of cognitive decline over the course of the study.

Coya is also pursuing combination therapies and has already done so in ALS, an exceptionally fast-progressing neurodegenerative disease, where treatment with Coya 302 (low-dose IL-2 + CTLA4 Ig) has been seen to stabilize disease progression. In the ALS study, patients experienced disease progression at 24 weeks and minimal reduction at 48 weeks, as measured by the ALSFRS (a commonly accepted operation for ALS). ALS patients typically decline at an average rate of more than one point/month on the ALSFRS-R. Already-approved drugs Relyvrio and Radicava slowed progression to -6.64 and -5.01 points, respectively, at six months on the ALSFRS-R score. Meanwhile, Coya 302 caused disease stabilization on the ALSFRS-R score (+.25 increase) at six months, with minimal decline noted at 12 months.

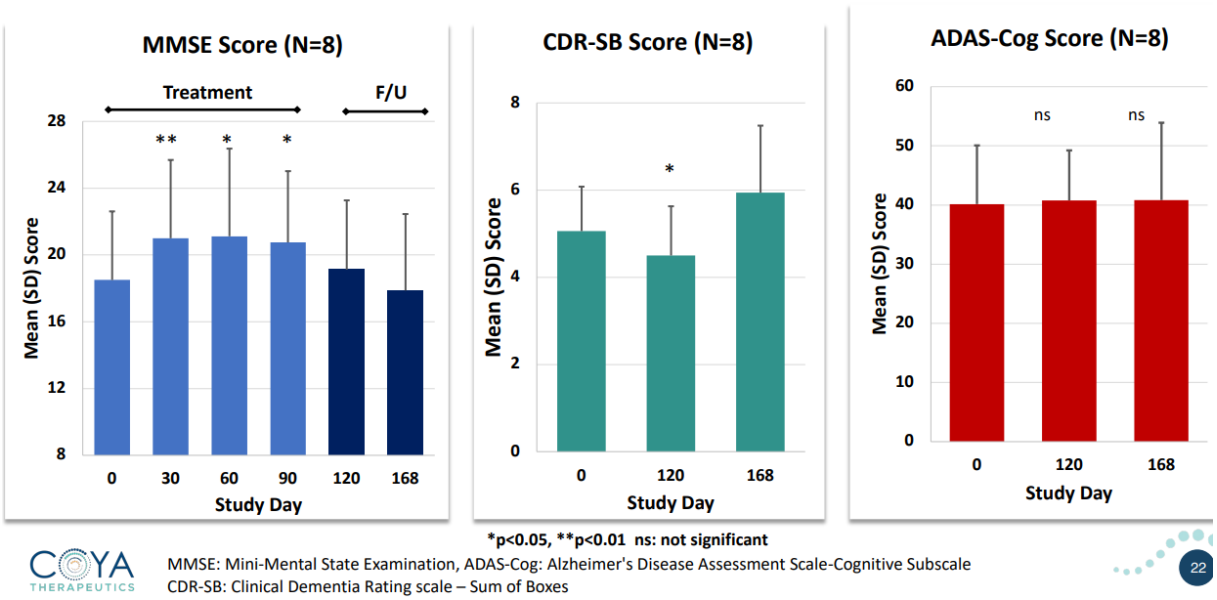
COYA 302: Appears to Ameliorate ALS Progression Over 48-weeks



Source: corporate presentation Coya Therapeutics.

In Alzheimer's, Coya Therapeutics measured the progression of patients over four months of treatment with Coya 301, with two months of follow-up with no further treatment. Coya 301 is looked at as backbone therapy and will probably be combined with another drug candidate in actual trials to result in higher efficacy. The following effect on cognition has been communicated to the public.

COYA 301 Improved or Halted Cognitive Decline in AD Patients

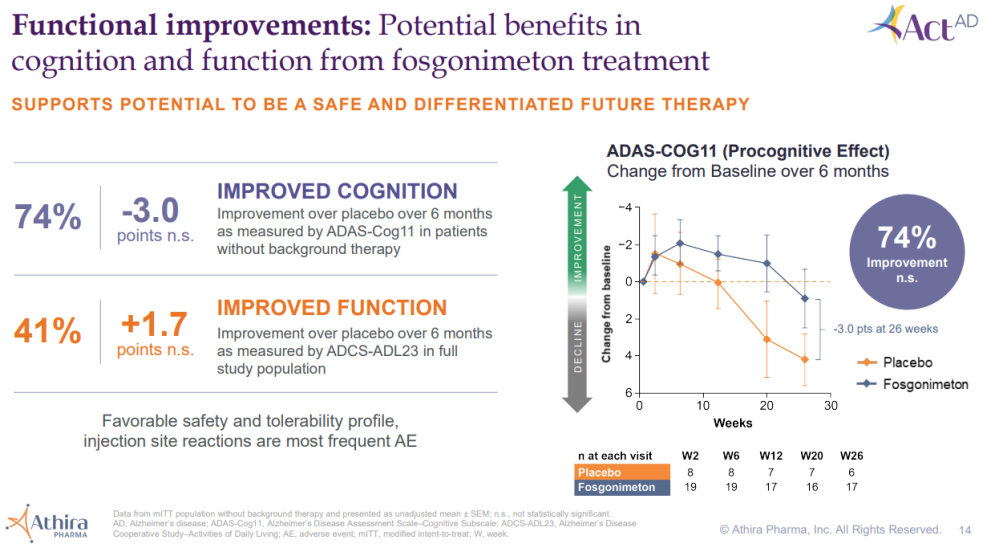


Source: corporate presentation Coya Therapeutics.

Of note, Coya Therapeutics also reported a correlation between effects on cognition and reduction of inflammation.

4.3.6 Side note: Athira Pharma's "failed" Phase 2 trial and ongoing Phase 2b/3 trial

Although Athira Pharma's Phase 2 readout was unimpressive in the overall study population, apparently due to its drug fosgonimeton's lack of synergy with acetylcholinesterase inhibitors, its data could be seen as interesting on a biomarker[21] and cognition level in the monotherapy population.



Source: Athira Pharma corporate presentation

Fosgonimeton is said to act on the HGF/MET pathway, which has been reported to activate signalingpathways to protect neurons from oxidative stress, excitotoxicity and apoptosis. Fosgonimeton is a positive modulator of the HGF/MET system, which Athira Pharma believes leads to reduction of inflammation and neuroprotection, among other effects, by modulating the activity of glial cells.

Of note, Athira Pharma has tweaked its ongoing Phase 2b/3 trial to overcome the issues seen in its Phase 2 trial. An unblinded interim efficacy and futility analysis by an independent committee has led the company to add fewer than 150 patients, for a total of fewer than 300 patients without background therapy (acetylcholinesterase inhibitors). That should allow the study to be well-powered for the primary endpoint. That Phase 3 trial should report data some time in 2024.

[21] Biomarkers of note reported: NfL, GFAP, YKL-40, AB-42/40 and ptau-181.

Source: corporate presentation.

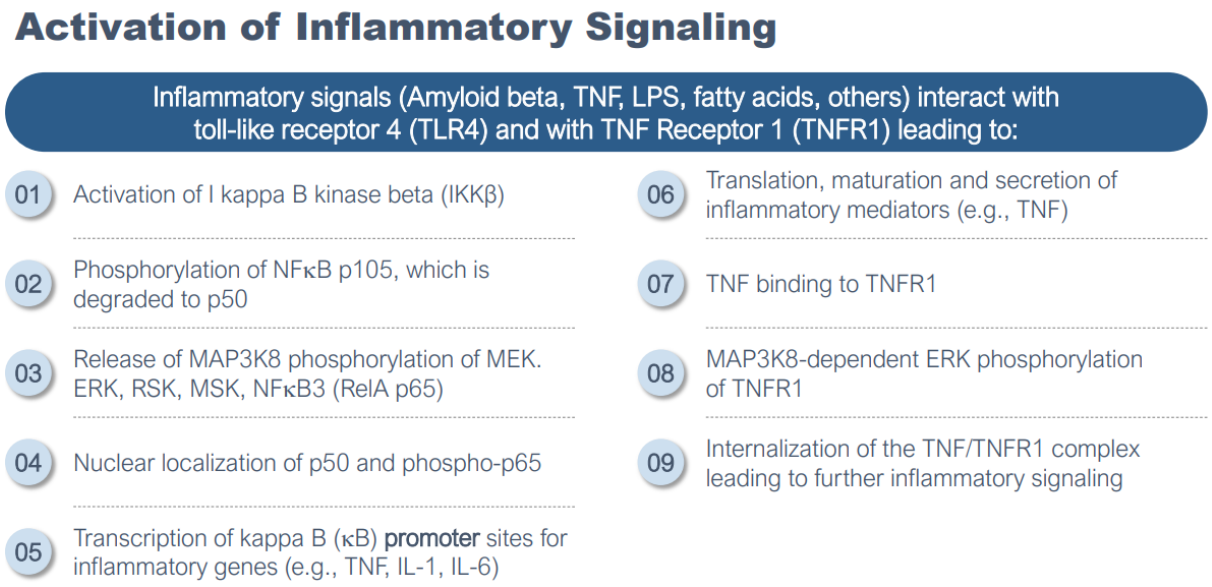
5. BioVie - NE3017

5.1. NE3107's mechanism of action

NE3107 has been widely tested, both clinically and preclinically. The results of such testing can, among others, be found in an overview document published by the Alzheimer's Drug Discovery Foundation.

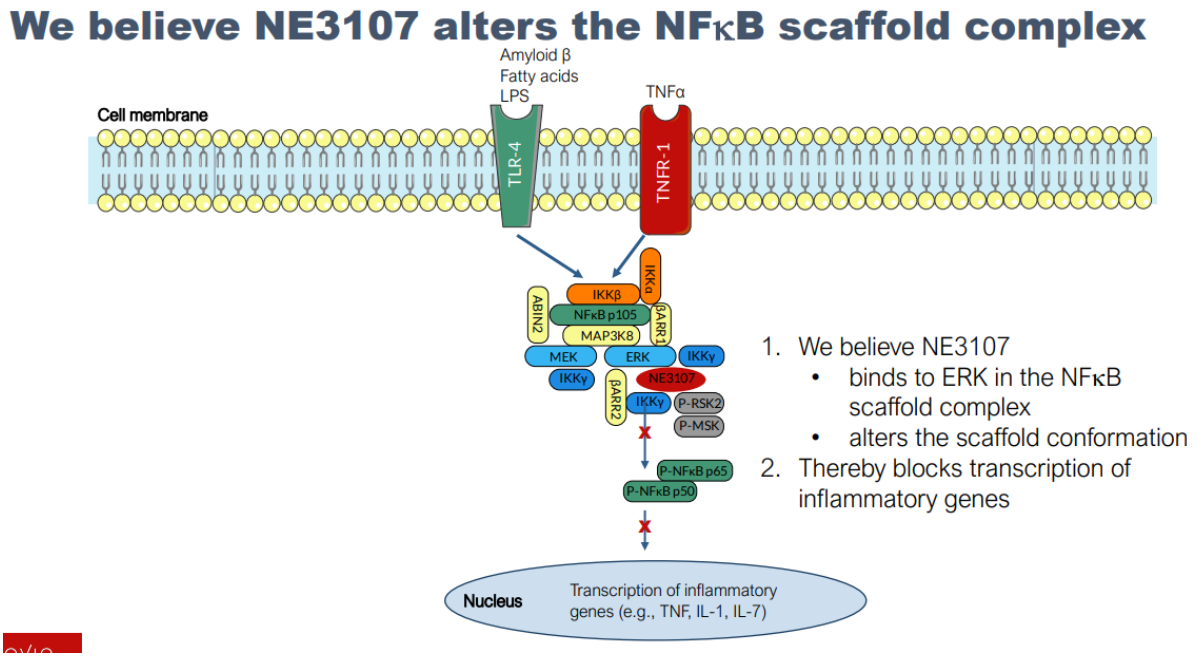
NE3107 is a selective insulin sensitizer and TNF inhibitor that reportedly does not inhibit homeostatic functions (e.g., insulin signaling, neuronal growth/protection). Non-selective inhibition of both ERK and NF-kB could lead to cell death and hence would not be fit for this purpose. NE3107 selectively inhibits ERK and NFκB. Inhibition of NFκB, a central regulator of pro-inflammatory cytokines, should reduce inflammation.

Inhibition of ERK should reduce insulin resistance, which leads to inflammation, which may, in turn, create more insulin resistance, and vice versa.



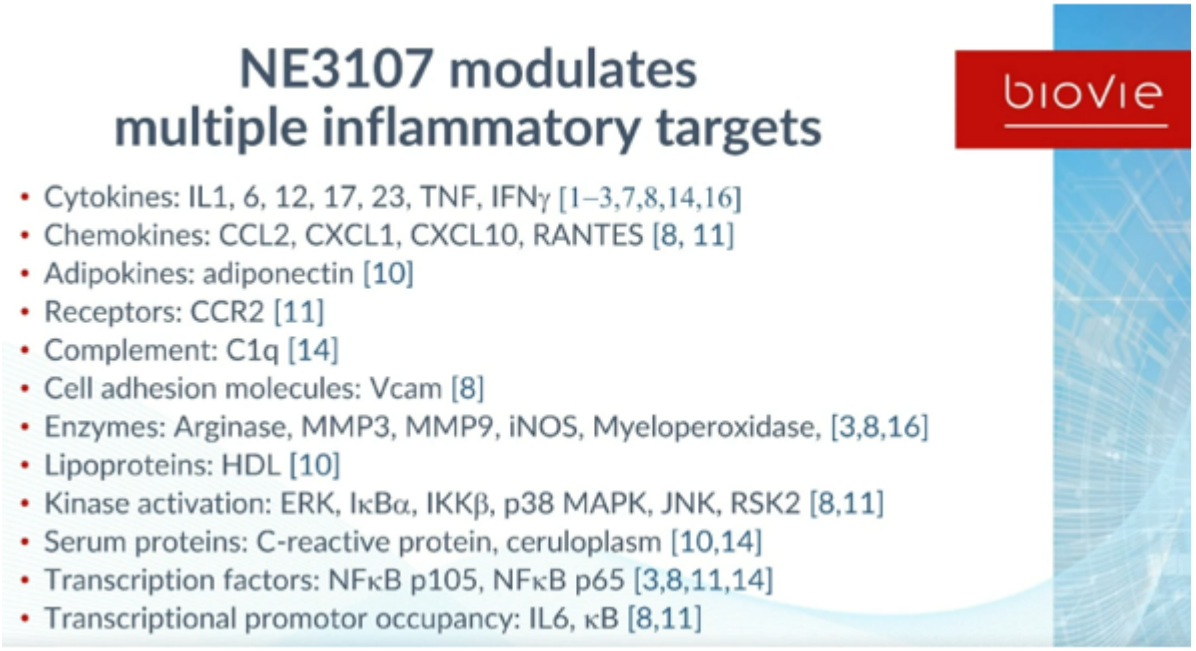
Source: corporate presentation BioVie, accessed June 2023.

NE3107 is reported to inhibit NF-κB by modulating the signaling pathways of the TLR4 receptor, which is triggered by amyloid-beta, fatty acids and lipopolysaccharides, and the TNFR-1 receptor, which is triggered by TNF. That modulated pathway would ultimately lead to inhibition of inflammatory factors such as TNF, IL-1, IL-7 and other chemokines.



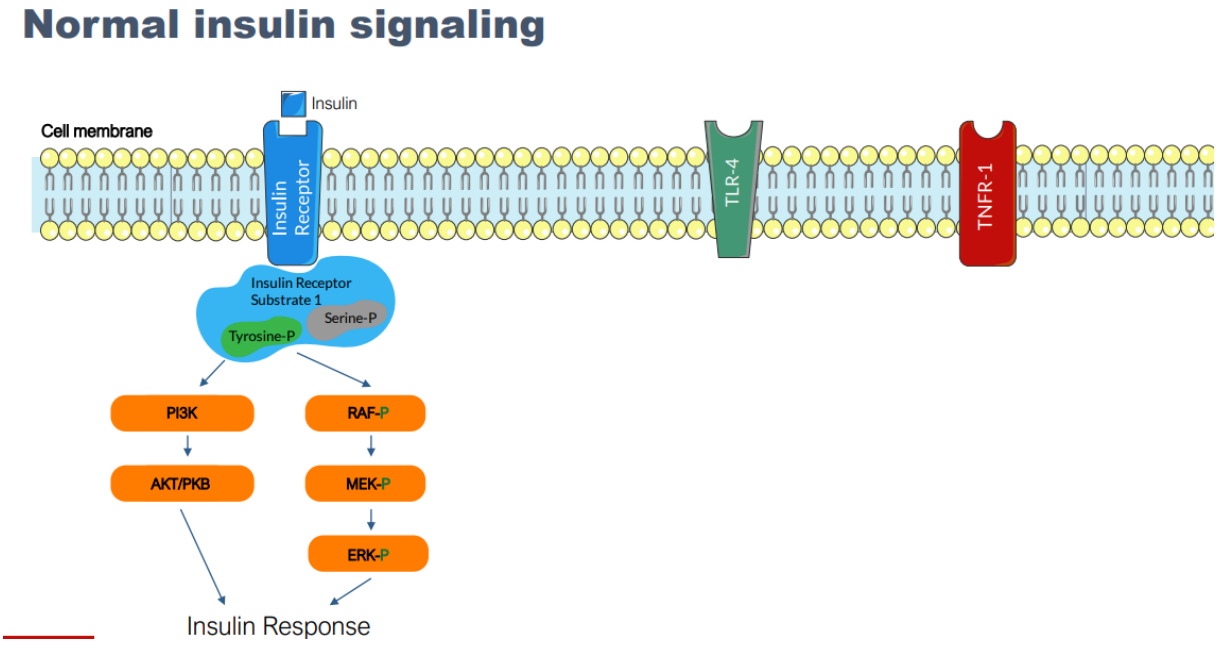
Source: BioVie Day presentation, corporate website BioVie.

NE3107 is indicated in red. Of note is the action of NE3107 through TNF receptor 1, not TNF receptor 2.

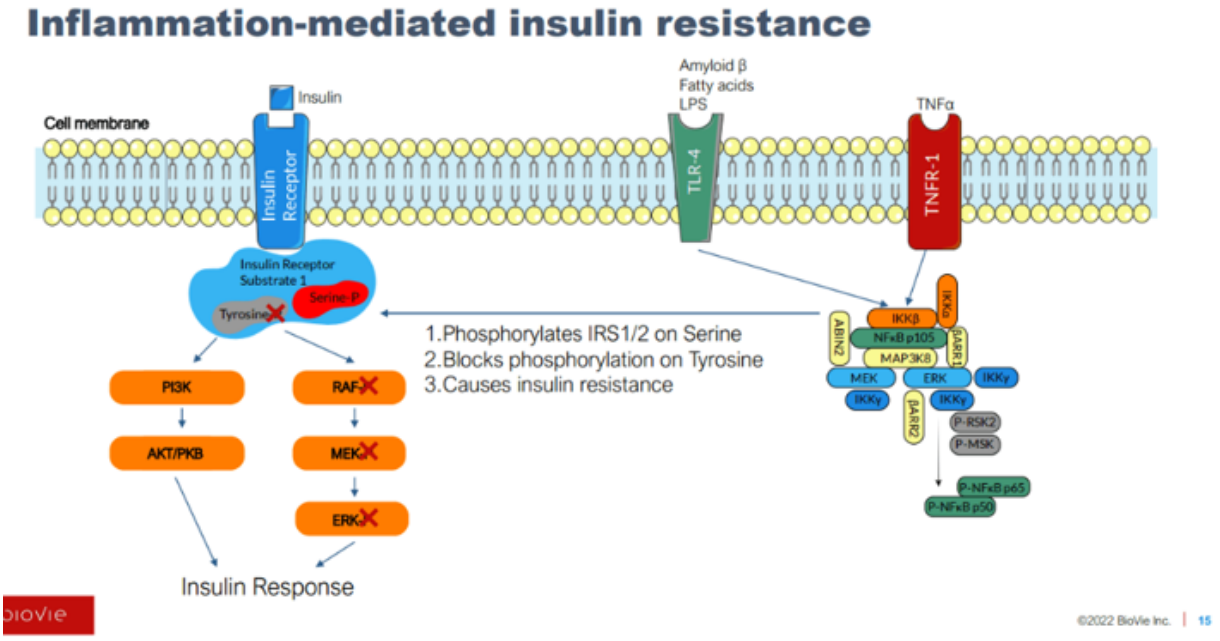


Source: BioVie R&D Day, corporate website BioVie.

NE3107 purportedly also changes the normal insulin signaling that's considered defective in AD, sometimes referred to as "Type 3 diabetes," by blocking the phosphorylation of serine, which, in turn, allows the phosphorylation of tyrosine and would allow a normal insulin response.



Source: BioVie Day presentation, corporate website BioVie.



Source: BioVie Day presentation, corporate website BioVie**.**

Previous clinical studies have also shown the effect of NE3107 on different insulin- and inflammation-related pathways.

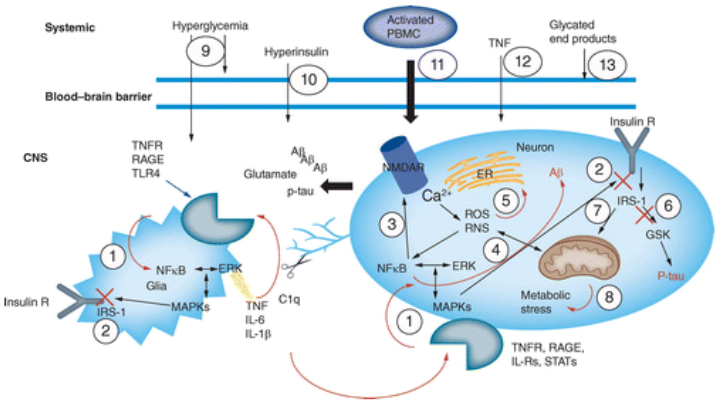


Figure 2. NE3107 inhibition of NF-κB-ERK pathological activation and associated MAP kinase activation has the potential to impact many of the major mechanisms of Alzheimer's disease pathophysiology, without inhibiting homeostatic functions.

The approach here is that, in light of the multiple pro-inflammatory triggers that can lead to chronic neuroinflammation as seen in neurodegenerative diseases, of which amyloid (aggregates) are one, inhibiting these pro-inflammatory triggers in the cell before they allow the production of TNF without affecting homeostatic functions is key.

5.2. Scientific background

NE3107 fully builds on the scientific understanding that Alzheimer's is a multifactorial disease caused by an array of factors, including oxidative stress, mitochondrial dysfunction, reduced glucose metabolism and insulin resistance, with inflammation as a major hallmark and treatment target. Its published rationale for Phase 3 explains that in further detail.

Chronic low-grade inflammation

- Inflammation is the result of the body's natural protective processes

Insults	Responders	Master Alarms	Pro-inflammatory factors
• Pathogens	• Blood proteins	• NFκB transcription factors	• Cytokines
• Trauma	• Platelets	• Oxidative stress	• Chemokines
• Ischemia	• Granulocytes	• Reactive oxygen	• Receptors
• Stress	• Monocytes	• Reactive nitrogen	• Complement factors
• Radiation	• Macrophages		• Metalloprotinases
• Obesity	• Microglia		• Cell adhesion molecules
• Cancer	• Endothelial cells		

- If insults and pro-inflammatory factors eliminated, pathology addressed
- If not, low grade chronic inflammation and associated insulin resistance ensues
- Inflammation and insulin resistance go hand-in-hand

NE3107 has a dual mechanism of action, being both an anti-inflammatory and an anti-diabetic. As an anti-diabetic, it fits in the framework of trials with other anti-diabetic drugs, including GLP-1 agonists,

as mentioned in footnotes 17 and 18. Not coincidentally, perhaps, NE3107 has also been shown to be effective in a small, placebo-controlled Phase 2 trial for Parkinson's.[22]

Inhibition of NF-κB as a central regulator of pro-inflammatory cytokines through TNFR-1 should reduce inflammation. The rationale for targeting inflammation in neurodegenerative diseases has been mentioned above and is the main focus of this research note.

As explained above, metabolic dysregulation, obesity and diabetes can be considered prime drivers of Alzheimer's disease. About 80% of all Alzheimer's patients have diabetes, which is characterized by insulin resistance. Insulin resistance leads to inflammation, which may, in turn, create more insulin resistance, and vice versa. As mentioned earlier, Alzheimer's is sometimes referred to as Type 3 diabetes and is reported to contribute to, among other issues, amyloid beta aggregation, tau phosphorylation and oxidative stress in Alzheimer's disease.[23] BioVie's baseline data of patients enrolled in its Phase 3 trial, released on June 26, 2023, fits in that framework, showing that the majority of patients in that trial had a high hip-to-waist ratio, hypertension and impaired glucose metabolism, and almost half of all the patients had some degree of insulin resistance.

5.3. Mechanistic similarities and differences

5.3.1. Activity through TLR4 and possibly CD14

NE3107's inhibition of NF-kB results from the blocking of a signaling pathway originating from TLR4 and TNF. The TLR4 pathway activated by LPS is linked to CD14, which is likely to be implicated as well here, as TLR4 is reported to bind LPS with the help of LPS-binding protein and CD14.

The TLR4 receptor is reported to lead to inflammatory cytokine release. TLR4 is expressed in microglia, astrocytes and oligodendrocytes as immune cells of the CNS, which are in a pro-inflammatory state in Alzheimer's and other neurodegenerative diseases. TLR4 is considered a target for the treatment of AD, whereby toll-like receptors and mostly TLR4 function as pattern recognition receptors to induce inflammation. TLR4 specifically recognizes lipopolysaccharide, a major contributor to diabetes and insulin resistance. Stimulation of TLR4 leads to inflammation by a complex cascade of processes involving, among others, IL-1, TNF, NF-kB and the MAPK signaling

[22] Exenatide, another GLP-1 receptor agonist, had in a Phase 2 study shown that it may slow the progression of Parkinson's. Neuraly's GLP-1 agonist NLY01 failed to report statistical significance in Parkinson's disease in March 2023.

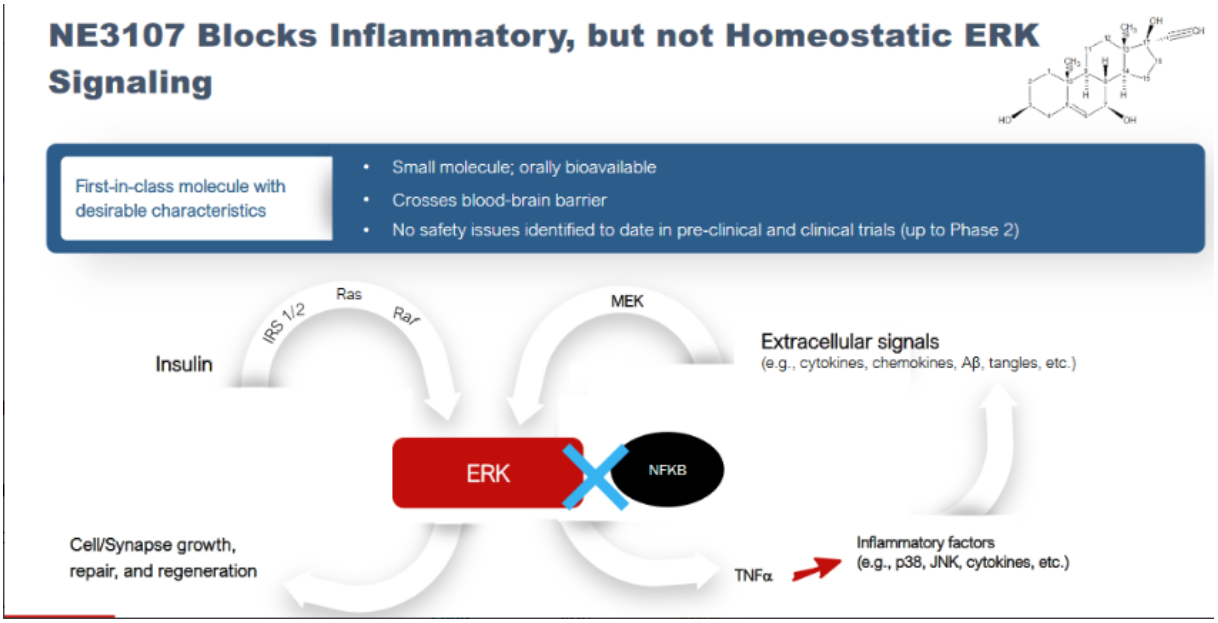
[23] In that framework, we remark that several anti-diabetics have also been tested for the treatment of both AD and PD. We highlight Neuraly's NLY01, a pegylated form of exenatide, a GLP-1 receptor agonist which is widely used for diabetes. GLP-1 agonists of Novo Nordisk and Eli Lilly have been in the news lately for their potential to reduce weight loss. GLP1 is a hormone that helps lower blood sugar levels, and stimulates insulin secretion. GLP-1 receptor agonists can help stabilize blood sugar levels. In preclinical models for AD and PD, NLY01 was able to inhibit secretion of neuroinflammatory cytokines by microglial cells, prevention the formation of neurotoxic A1 astrocytes, limit neuronal cell death, limit loss of motor function, increase survival, and improve spatial learning and memory. Neuraly's small placebo-controlled Phase 2 study in Parkinson's disease may have come close. It did not reach statistical significance for the entire patient population, though it did for the patient group under 60 years which accounted for 37% of the patient population, in which a clinically significant (and strong) reduction of approximately 5-points in the sum of UPDRS Parts II and III was noted after 36 weeks of treatment at 36 weeks ($p<0.01$ vs. placebo). The effect appeared to be dose-related and persistent over eight weeks after treatment was discontinued.

pathway which includes ERK, JNK, and p38. TLR4 is expressed more in APOE4-positive individuals. APOE4, a gene responsible for lipid transport, is the highest risk factor for AD. The APOE4 allele is linked to and mediates inflammation and neurodegeneration, and promotes formation of amyloid plaques.

5.3.2. Anti-inflammatory through inhibition of ERK and JNK

NE3107 purportedly selectively inhibits ERK and JNK, thereby not affecting their homeostatic functions.

ERK and JNK kinases are reported to be activated to phosphorylate tau.



Source: BioVie corporate presentation, accessed June 2023.

BioVie expressly states that homeostatic ERK signaling, leading to cell/synapse growth, repair and regeneration, is not blocked. The goal is to block inflammatory ERK and not block homeostatic ERK signaling. [24]

5.3.3. Selective inhibition of NF-kB signaling by NE3107 through TNFR1

5.3.3.1. NF-kB signaling in AD

NF-kB signaling has been reported to have a critical role in the pathogenesis of AD by being activated through TLR2, TLR4 and CD14, as it facilitates the production of several factors that constitute AD

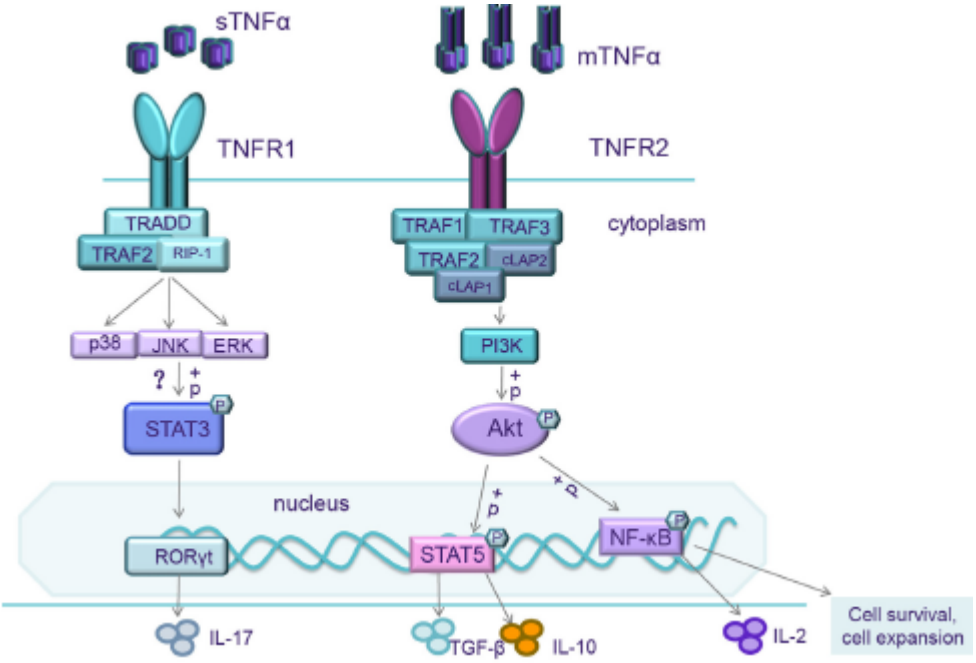
[24] BioVie's CEO stated in this regard on March 23, 2023, during BioVie Day: "*But unfortunately that is much easier said than done, because dozens of teams over several decades tried to do that, but all of those efforts failed due to toxicity. So what was really happening with all those different molecules is that it [they] became an active ERK inhibitor and was touching the insulin signaling component of ERK's role and was not only limited to inflammatory ERK.*"

pathology, such as amyloid plaques, neurofibrillary tangles and neuroinflammation. Its inhibition may therefore be useful for the treatment of neurodegenerative diseases.[25]

5.3.3.2. Two TNF receptors with different functions: TNFR1 and TNFR2

There are two TNF receptors, TNFR1 and TNFR2 with different opposing functions. Whereas TNFR1 primarily mediates inflammation and apoptosis, activation of TNFR2 mainly promotes cell proliferation and survival. The different functions of TNFR1 and TNFR2 have also given rise to the idea of developing TNFR2 agonists.[26]

The pathways of TNFR1 and TNFR2 are different.

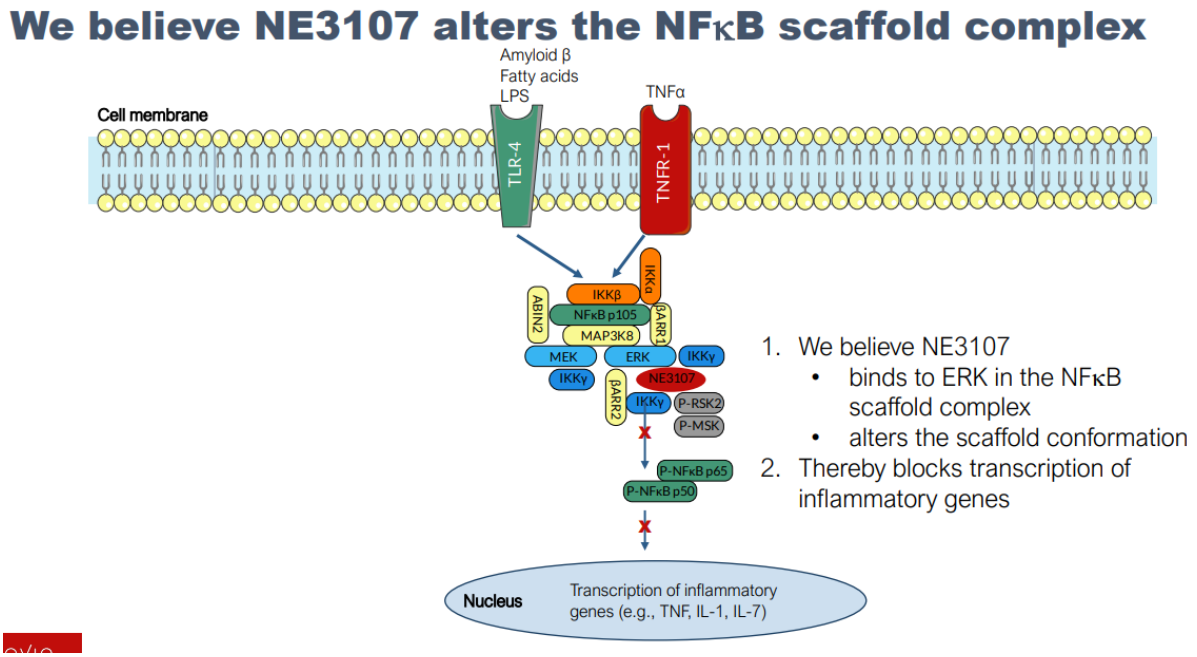


Source: S.G. Zheng et al., Role of TNF–TNF receptor 2 signal in regulatory T Cells and its therapeutic implications, Frontiers in Immunology, 2018.

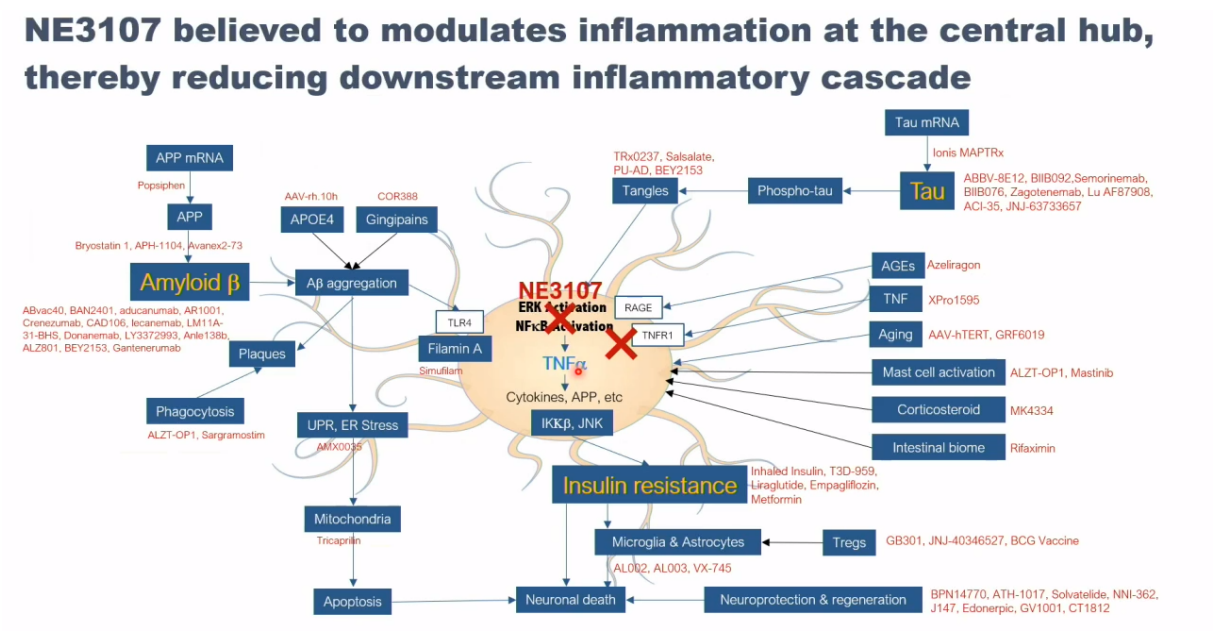
NE3107 inhibits JNK and ERK signaling in TNFR1, which leads subsequently to (selective) inhibition of NF-kB and reduction of inflammatory factors.

[25] Panax Ginseng, studied in Asian countries as a tonic for longevity, has been suggested as a treatment for Alzheimer's disease as different studies have shown its potential to improves AD symptoms and cognition. Ginseng is reported to work by activating macrophage through transcription factors NF-kB and AP-1 and their upstream signaling enzymes ERK and JNK. Ginseng has also been reported to improve cognitive deficit through inhibition/reduction of the inflammatory RAGE/NF-kB pathway, and the reduction of oxidative stress. Other medicinal plants such as *Pueraria thunbergiana Benth*, *Belamcanda chinensis* and *Iris unguicularis* have also been reported to exert their effect through downregulation of inflammatory mediators such as TNF-α and IL-6 by suppressing NF-κB/ERK/JNK-related signaling pathway.

[26] A TNFR-2 selective agonist has been reported to rescue human neurons from oxidative stress-induced cell death. TNFR-2 selective agonism has also been considered to proliferate Tregs.



Source: BioVie Day presentation, corporate website BioVie.



Source: BioVie Day presentation, corporate website BioVie.

Remark also the second red cross, indicating inhibition of TNFR1 signaling, and the connection to XPro1595 (INmune Bio).

The non-inhibition of TNF-signaling through TNFR2 may allow homeostasis.

5.3.3.3. Two types of TNF with two different functions: soluble and transmembrane TNF

There are two two types of TNF, soluble TNF and transmembrane TNF. Transmembrane TNF is active in innate immune defense against infection and in myelination. Once cleaved to a soluble form, TNF becomes a mediator of inflammatory processes. Soluble TNF leads to apoptosis.

Soluble TNF signals solely through TNFR1. Transmembrane TNF signals primarily through TNFR2. Soluble TNF can bind to TNFR1 and 2, but TNFR2 but needs transmembrane TNF for robust activation.

5.3.3.4. Possible similarity with inhibition of soluble TNF

The selectivity of NE3107 through TNFR1 may rebalance anti- and pro-inflammatory and survival processes, and may allow defense against infection and myelination. As TNFR2-signaling should remain unaffected by NE3107, the positive effects of transmembrane TNF, which primarily binds to TNFR2, may be left unaffected whereas the detrimental effects of soluble TNF signaling through TNFR1 may be inhibited. In that sense, NE3107 may be having an effect that is similar, to some degree, to INmune Bio's XPro. If so, the extent of such similarity and the level of efficacy of both drug candidates in doing what they're supposed to do is unclear. Directly targeting soluble TNF may exert stronger anti-inflammatory effects.

5.3.4. Improved insulin receptor signaling involving IRS

NE3107 binds to ERK1/2, which are kinases involved in inflammatory signaling and insulin responses. Insulin resistance is the key hallmark of type 2 diabetes, and seems to be a driver of Alzheimer's disease as well, including impaired insulin signaling and oxidative stress.

NE3107 was originally developed as an anti-diabetic agent. In a phase 2 trial in diabetes in humans, NE3107 either as monotherapy or in combination with metformin decreased insulin resistance, with effects being different depending on whether patients were treatment naïve or had been treated with metformin previously, and also whether inflammation was present at baseline. These results suggested that NE3107 targeted the impairment in the insulin receptor signaling pathway causing chronic low-grade inflammation. A preclinical study in a rat model had reported that NE3107 downregulated inflammatory cytokine/chemokine expression in the liver and adipose tissue, normalized fasting and non-fasting glucose levels, improved glucose tolerance, and enhanced insulin sensitivity in the skeletal muscle and liver.

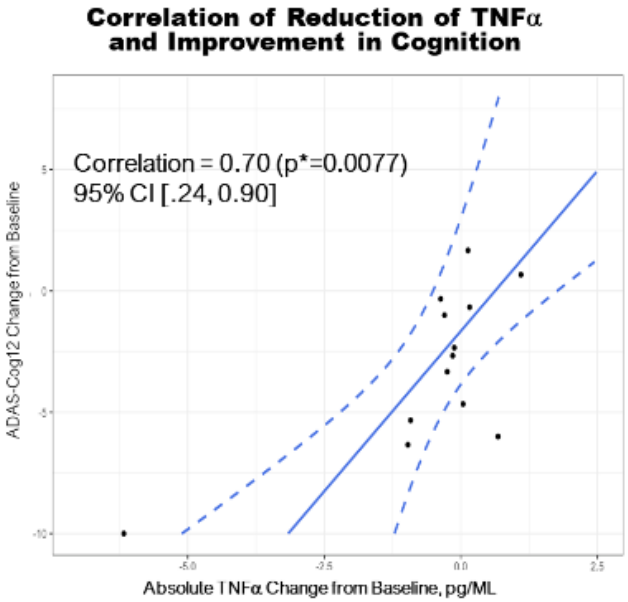
Inhibition of ERK, a major regulator of pro-inflammatory microglial activation in Alzheimer's, should lower insulin resistance. Insulin regulates energy delivery. Insulin signaling is less efficient in patients with impaired glucose tolerance and Type 2 diabetes. Up to 81% of AD subjects have impaired glucose tolerance and type 2 diabetes. Insulin resistance leads to an inflammatory loop.

5.3.5. Biomarkers

At three months, NE3107 reduced CSF phospho-tau levels by -1.66 pg/mL (p=0.0343), including a reduction by 5% in MCI/mild AD patients.

NE3107 reduced the ratio of p-tau to A42 by -0.0024 (p=0.0401).

A significant correlation was found between cognitive results and reduction in TNF.



Source: BioVie corporate presentation, accessed June 2023.

5.3.6. Potential to stabilize cognitive decline

NE3107 treatment at three months in an open label study showed the potential to enhance cognition as measured by multiple cognitive rating scales, including a 2.2 point improvement (p=0.0173) on the modified ADAS-Cog12 scale equating to a 21.1% (p=0.0079) change compared to baseline and a 0.11 point improvement (p=0.0416) on the Clinical Dementia Rating scale (CDR), equating to 19.4% (p=0.0416) change from baseline.

5.3.7. Responder heterogeneity

The cognitive scoring over three months' time and biomarker results suggest that there is heterogeneity in the treatment response by patients.

5.3.8 Systemic normalization / anti-aging

As mentioned above, preventing glia from exacerbating neuroinflammation, while allowing them to execute homeostatic and nurturing functions may be key.

BioVie has reported that NE3107 treatment for 3 months resulted in a reduction of 3.3 years on the Horvath DNA methylation SkinBlood epigenetic clock compared to baseline (p=0.0021), consistent with the reported association between TNF as master regulator of inflammation and DNA hypermethylation. This may be indicative of normalization of metabolic and inflammatory values.

Furthermore, patients treated with NE3107 for 3 months saw >50% reductions in the level of DNA methylation of over 400 CpGs, which are sites on DNA strands where DNA can be "methylated." Correlations were established between reduction of DNA methylation and cognitive improvements and several biomarkers including TNFα, CSF p-Tau/Aβ 42 , and precuneus glutathione. Associations to genes related to antioxidation, insulin signaling, anti-inflammation, anti-apoptosis, anti-amyloid and

neurostimulation were found. In total, over 3,000 statistically significant correlations were found between reductions in DNA methylation of various CpGs and cognitive, biomarker and neuroimaging endpoints (presentation available here). That press release came on the day the Alzheimer's foundation considered that novel therapies were needed focused on the biology of aging.

5.3.9. Safety

NE3107 appears to have a seemingly safe profile, and no serious side effects have been reported so far.

5.3.10. Fast onset

NE3107 seems to have a fast onset compared to anti-amyloid therapies.

5.3.11. No infusion

NE3107 can be taken in the form of a pill.

5.3.12. Dual mechanism of action

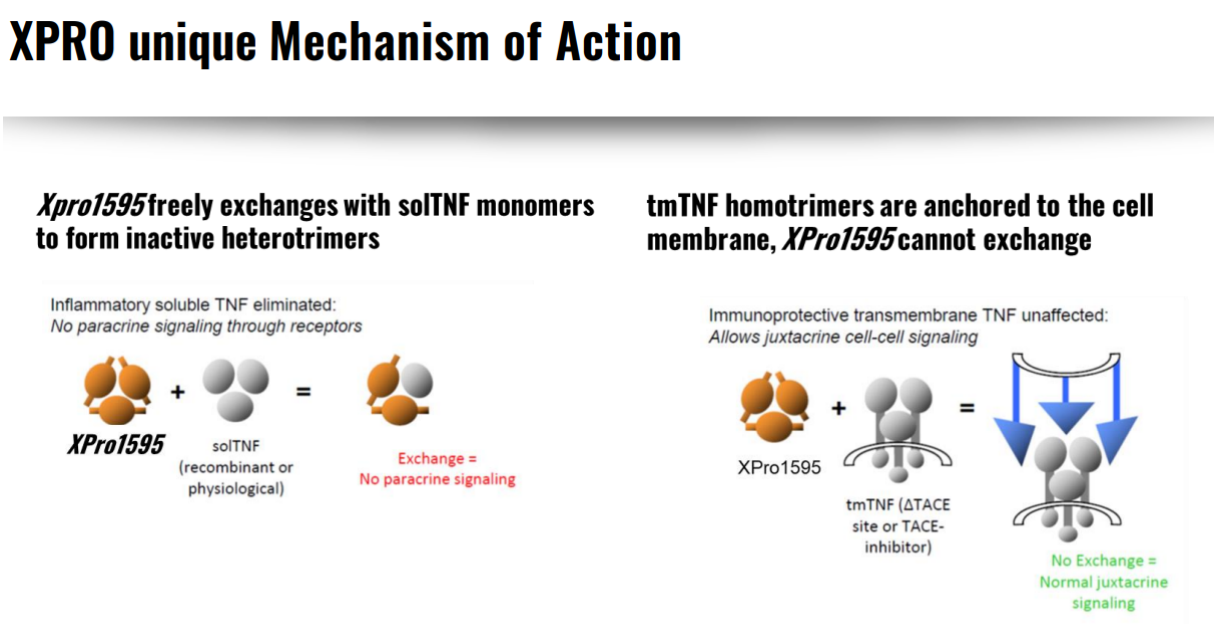
NE3107 is reported to modify Alzheimer's disease both by reduction of tau phosphorylation and by lowering chronic neuroinflammation.

6. INmune Bio's XPro

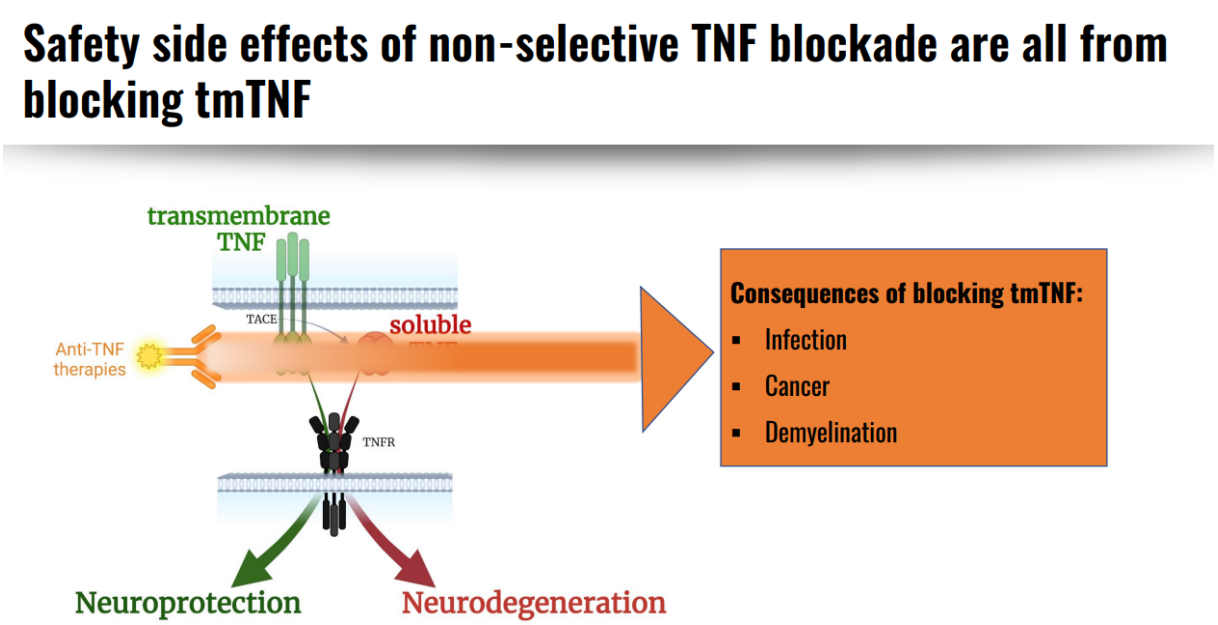
6.1. XPro's mechanism of action

TNF inhibitors have been approved since 1998 for various diseases, but come with the downside of suppression of immunity and neurological issues. They are not allowed for use in diseases of the central nervous system.

XPro1595 is a second-generation TNF inhibitor that is selective in that it only targets soluble TNF, but not transmembrane TNF. XPro selectively blocks soluble TNF, which is considered the 'bad' TNF. The good TNF, transmembrane TNF, is bound to the cell membrane. Soluble TNF is thereby blocked from binding to TNF receptors.



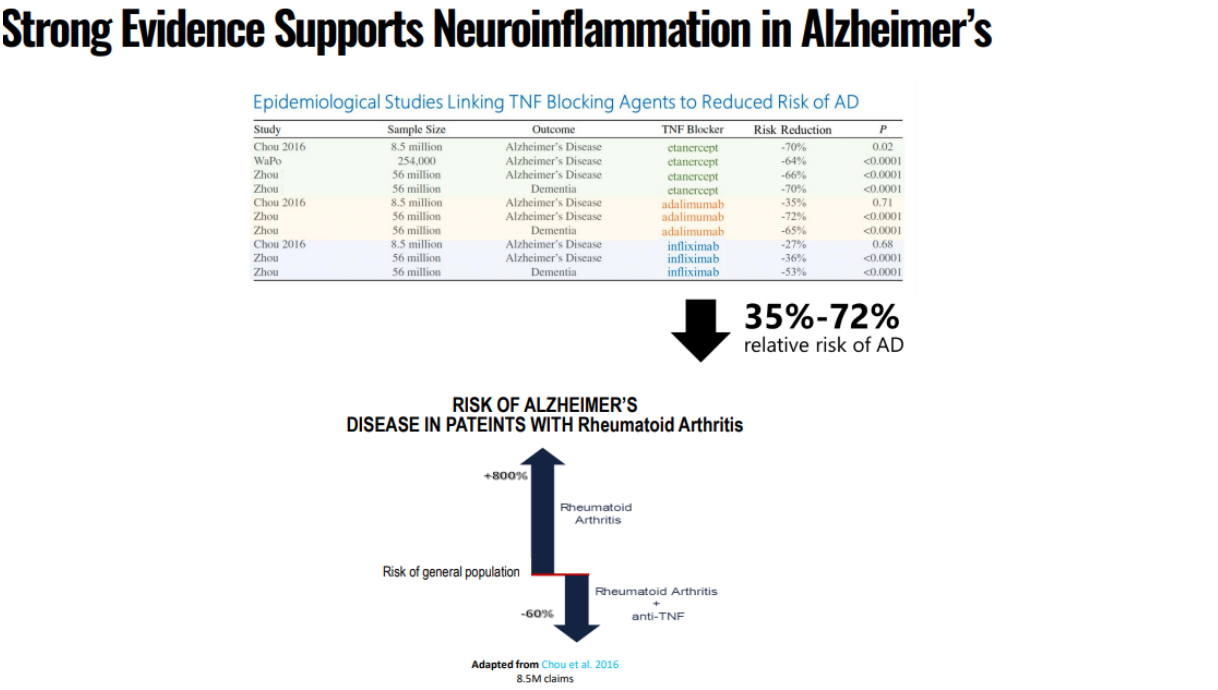
Source: INmune Bio corporate presentation, accessed June 2023.



Source: INmune Bio corporate presentation, accessed June 2023.

6.2. Scientific background

Like BioVie, XPro fully builds on the scientific understanding that Alzheimer's is a multifactorial disease with inflammation as a major hallmark and treatment target.



Source: INmune Bio corporate presentation, accessed June 2023.

Systemic TNF is associated with more rapid cognitive decline in Alzheimer's patients.

INmune Bio's website features 81 publications in which XPro has been tested in different disease models. Some of these preclinical results showed, among others:

- treating with Xpro of an amyloid transgenic mouse model before amyloidosis prevented synaptic deficits otherwise apparent at the age of 6 months;
- peripheral administration of XPro modifies brain immune cell profiles, decreases beta-amyloid plaque load, and rescues impaired long-term potentiation in 5xFAD mice;
- inhibition of soluble TNF with XPro may slow the appearance of amyloid-associated pathology, cognitive deficits, and potentially the progressive loss of neurons in AD;
- decreased neurogenesis by long-term inhibition of TNF with a nonselective TNF inhibitor, contrary to treatment with XPro in mice hippocampi;
- remyelination by affecting astroglial and microglial biology.

6.3. Similarities and differences in mechanism of action

6.3.1. Anti-inflammatory activity through TLR4

XPro was seen to preserve myelin integrity in mice with spinal cord injury via the upregulation of TNFR2 and TLR4 expression. TLR4 was furthermore considered to mediate neuroinflammation through soluble TNF signaling in a rat model of opioid tolerance.

6.3.2. Anti-inflammatory activity through inhibition of ERK and JNK

It has been reported that, by preventing soluble TNF signaling, the intracellular downstream signaling cascade involving p38, JNK and ERK was also inhibited.

6.3.3. Anti-inflammatory activity through inhibition of NF-kB signaling

As explained above, inhibition of soluble TNF, often referred to as the "bad" TNF, by XPro may have an effect similar to the inhibition of NF-KB through TNFR1 signaling by BioVie's NE3107.

There are two TNF receptors, TNFR1 and TNFR2. TNFR1 and TNFR2 do not have identical pathways or functions. While TNFR1 primarily mediates inflammation and apoptosis, activation of TNFR2 mainly promotes cell proliferation and survival.

There are also two types of TNF: soluble TNF and transmembrane TNF. Transmembrane TNF, the so-called "good" TNF, signals primarily through TNFR-2 and is active in our innate immune defense against infection and in myelination. Soluble TNF leads to apoptosis and signals through TNFR-1 and TNFR-2. Once cleaved to a soluble form, TNF becomes a mediator of inflammatory processes. The overlap and different effects of TNF on different pathways can impact insulin sensitivity.

Inhibition of soluble TNF may rebalance tightly regulated anti- and pro-inflammatory processes. When soluble TNF cannot bind TNFR1 or 2, there may be less inflammatory signaling through both receptors.

In a mice-induced model of multiple sclerosis, the therapeutic benefit of XPro was dependent on the activity of NF-kB. In a rat model of traumatic brain injury, the ADAM17/solTNF-α/NF-κB pathway was reported to play an important role in the subsequent inflammatory response and tissue injury: "*When*

solTNF interacts with receptors on the surface of the cell membrane, the receptors activate RIP, which eventually activates IKK kinase by phosphorylating and dissociating the NFκB-α protein from the trimer. Subsequently, the NF-κB dimer is exposed to a nuclear localization sequence (NLS), and phosphorylated p65 rapidly enters the nucleus from the cytoplasm, where it binds to a specific sequence on nuclear DNA and promotes the transcription of related genes. The NF-κB pathway is associated with the expression of numerous cytokines and is involved in the regulation of the inflammatory response, apoptosis and other pathophysiological processes through direct or indirect intercellular signaling pathway interactions."

In that sense, NE3107 may have an effect that is similar, to some degree, to INmune Bio's XPro. If so, the extent of such similarity is unclear. Directly inhibiting soluble TNF may exert a stronger effect.

6.3.4. Improved insulin receptor signaling

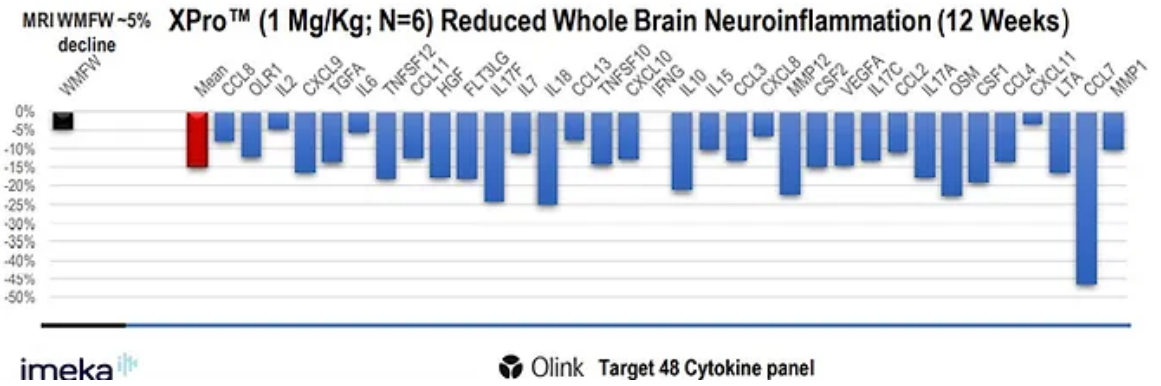
Prior to the pandemic, INmune Bio's focus with XPro ("Livnate") had also been on nonalcoholic steatohepatitis (NASH), a well-known liver disease. INmune Bio's 2020 annual report mentioned in that regard: "*The company views NASH as a disease of chronic inflammation caused by three inflammatory loops. The peripheral inflammatory loop is due to obesity and insulin resistance. The regional inflammatory loop is due to intestinal inflammation and mesenteric fat. The local inflammatory loop is due to lipotoxicity and innate immune activation*."

In murine models of NASH, XPro was reported to have effects on each pathologic cycle, decreasing insulin resistance, intestinal inflammation and leak, hepatic inflammation, hepatocyte death, and fibrosis. INmune Bio expected these results to be confirmed in humans.

6.3.5. Biomarkers

XPro has improved multiple biomarkers of neuroinflammation, neurodegeneration, microglial activity, neuronal plasticity and Alzheimer's.

XPro reduced an entire panel of biomarkers of neuroinflammation after three months.



Source: INmune Bio corporate presentation, accessed June 2023.

Treatment with XPro:

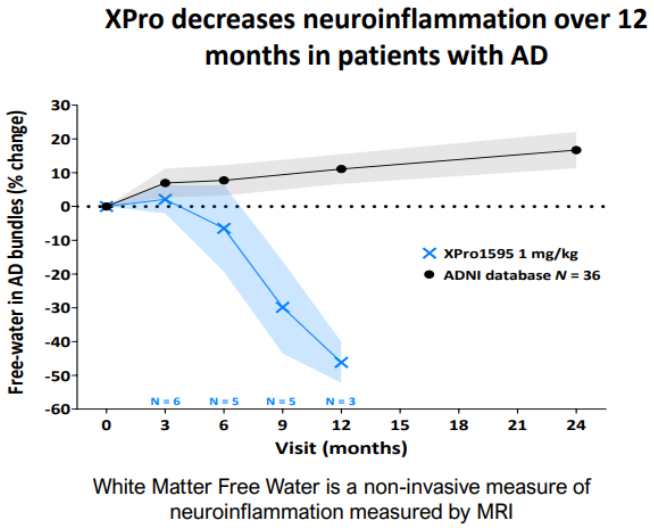
- Decreased c-reactive protein (CRP) & YKL-40;

- Showed decreased neuroinflammation based on MRIs of white matter free water, a validated biomarker of neuroinflammation;

- Decreased neuroinflammation in the arcuate fasciculus, a major white-matter bundle, by 40% as reported in patients treated with XPro, versus a 4.6% increase in the reference cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

XPRO DECREASES NEUROINFLAMMATION IN AD

Decrease in Neuroinflammation in white matter tracts over 12 months



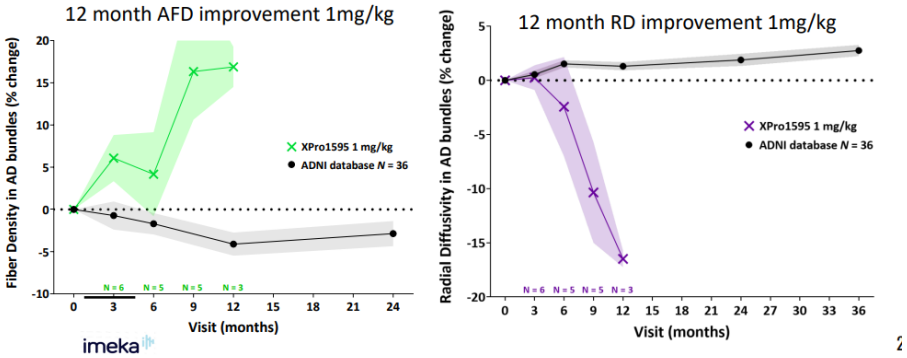
Source: INmune Bio corporate presentation, accessed June 2023.

- Was reported to decrease p-tau217 by 46% ($p<0.0001$), with a smaller reduction in p-tau181. Notably, p-tau217 is the more novel and more specific biomarker;

- Was reported to improve axonal integrity and remyelination, with results improving over the course of 12 months:

THE "DOWNSTREAM" BENEFITS OF XPRO™ IN PATIENTS WITH ADI

- XPRO improves axonal integrity in white matter tracts (increased AFD)
- XPRO promotes remyelination/myelin repair (RD)



Source: INmune Bio corporate presentation, accessed June 2023.

- Decreased the neurodegeneration markers neurogranin, neurofilament light (NFL) and visinin-like protein 1 (VILIP-1) by 84%, 56% and 91%, respectively, at three months;

- Increased synaptic protein contactin-2 by 222% at three months;

- Led to a 16% improvement in radial diffusivity, a biomarker of remyelination;

- Led to a 6% improvement in gray matter over the course of nine months – the furthest datapoint collected – and a 13% improvement in 31 out of 33 white-matter bundles;

- Led to a dose-dependent enhancement in gray matter measures using the novel biomarker PerpPD+, which was reported to be more specific than standard whole-brain volumetric changes in predicting cognitive decline. The greatest improvement was observed in the brain regions where Alzheimer's disease originates, and PerpPD+ baseline levels are highly correlated with baseline levels of cerebral spinal fluid biomarkers of AD pathology (amyloid and tau), inflammation (YKL-40, GFAP and sTREM2), and cognitive status (MMSE scores).

6.3.6. Potential to stabilize cognitive decline

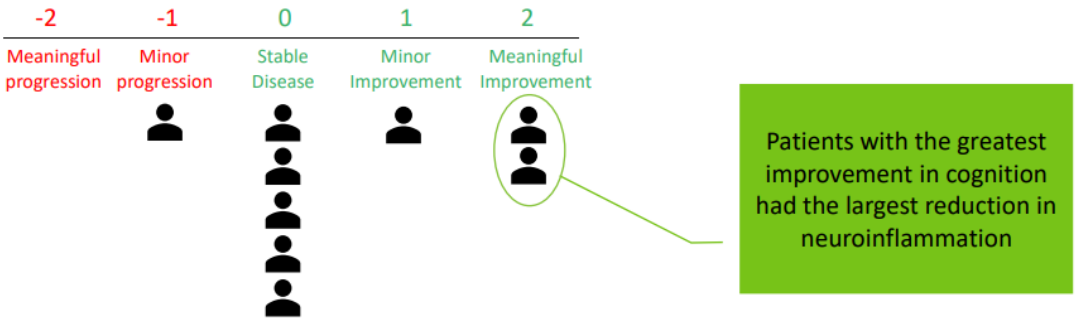
At this time, INmune Bio has only shared anecdotal information on patients in its Phase 1 study, from which it would appear that XPro may stabilize or reverse cognitive decline. All patients from the Phase 1 study have requested to be placed on trial again.

Cognition in patients in the Phase 1 trial was tested. INmune Bio has not shared this information yet, but a correlation between improved cognition and reduced neuroinflammation was established:

Clinical Benefit in Phase I trial

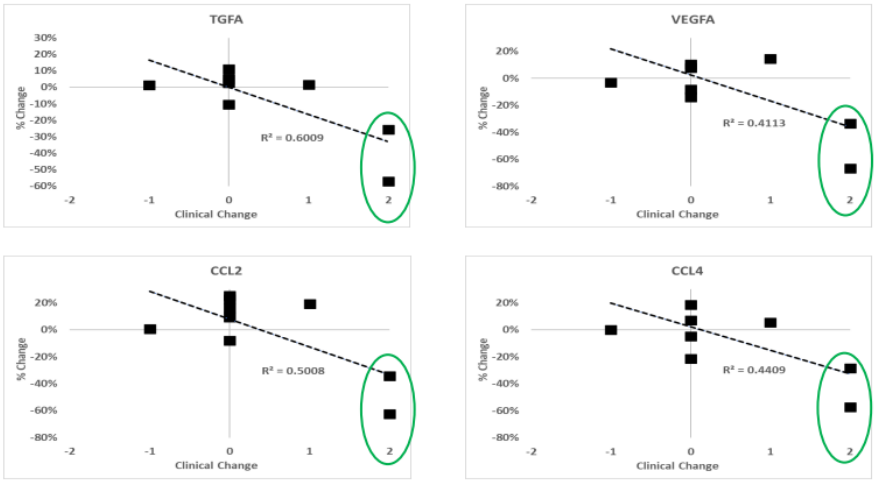
Disclaimer: small N, disease status heterogeneity, short time period

- Assessments administered:
  - Cognitive: MMSE, Verbal Fluency Test, Digit Symbol Coding
  - Neuropsychiatric Inventory
  - Bristol Activities of Daily Living Scale
- To compare across patients of different disease states, Dr. Judith Jaeger issued each patient a qualitative score of (-2, -1, 0, 1 ,2) based on her assessment of the overall change over 3 months.



Source: INmune Bio corporate presentation, accessed June 2023.

Correlation between decreased neuroinflammation and improved cognition



R^2 = 0.4 to 0.6
CSF cytokines by OLINK platform

Source: INmune Bio corporate presentation, accessed June 2023.

Of note, the words “improved cognition” are mentioned on both slides.

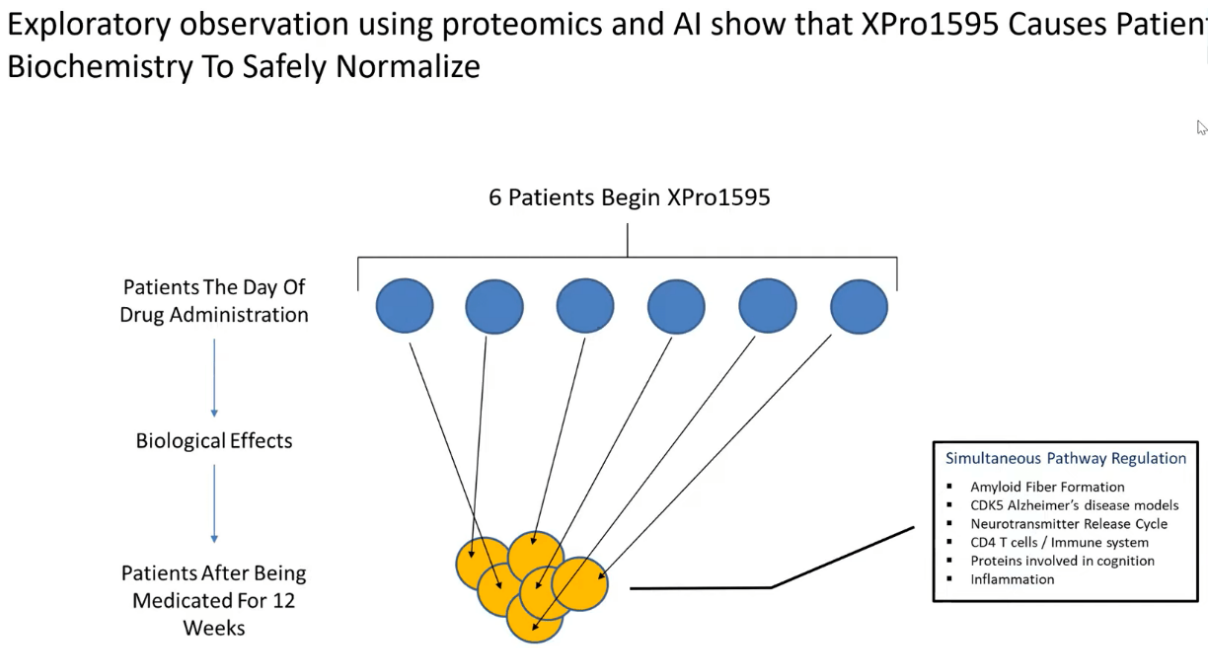
6.3.7. Responder heterogeneity

The cognitive scoring and biomarker results suggest there is heterogeneity in the treatment response by patients.

6.3.8 Systemic normalization / homeostasis / anti-aging

As mentioned above, preventing glia from exacerbating neuroinflammation while allowing them to execute homeostatic and nurturing functions may be key.

INmune Bio has reported that patients in its Phase 1 trial saw systemic normalization of their biochemistry.



Source: INmune Bio first webinar on Phase 1 results.

The underlying thesis to INmune's approach is that diseases of aging are the result of chronic inflammation, sometimes referred to as "inflammaging," meaning persistent, low-grade inflammation that develops with advancing age, independent of apparent infections. This chronic inflammation could then exacerbate other age-related conditions. In the framework of Alzheimer's, cognitive aging, or a gradual decline in cognitive function starting in the mid-50s and accelerating after 65, is most in focus. Although Alzheimer's is a well-defined disease that often sets in later in life, INmune Bio sees cognitive aging linked to inflammation as a disease resulting from the culmination of genetic (ApoE4 gene), epigenetic (diabetes, cardiovascular, autoimmunity), behavioral (obesity, smoking, sedentary living, diet), environmental (pesticides, pollution), and biologic (cellular senescence) factors. On July 17, 2023, INmune Bio presented an opening keynote speech at the 5th World Aging and Rejuvenation Conference on drug development strategies to improve one's lifespan by treating chronic diseases of aging.

6.3.9. Safety

XPro appears to have a seemingly safe profile, and no serious side effects have been reported so far.

6.3.10. Fast onset

XPro seems to have a fast onset compared to anti-amyloid therapies.

6.3.11. No infusion

XPro can be taken in the form of a patch.

6.3.12. Potential dual mechanism of action

XPro works by inhibiting soluble TNF. As such, that appears to be a single mechanism of action. However, as will be shown below, inhibition of soluble TNF leads to downstream effects similar to what has been seen with simufilam and NE3107, including an effect on insulin signaling.

7. Cassava Sciences' simufilam

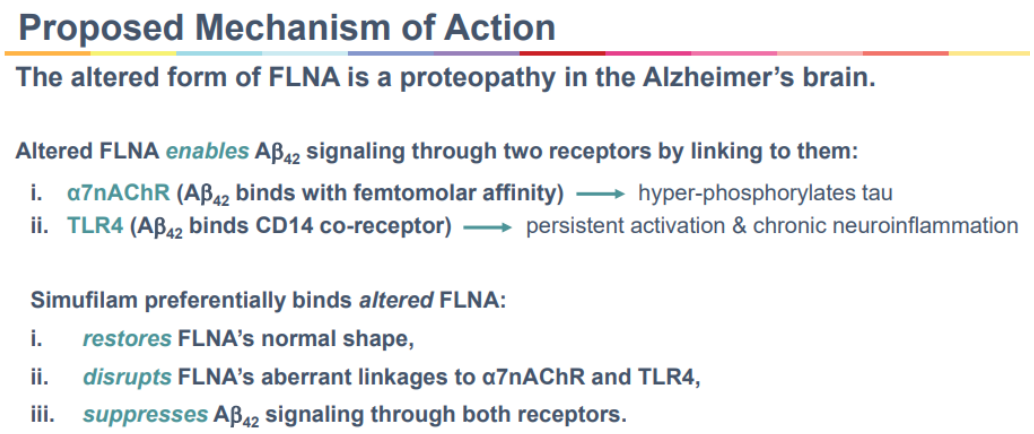
7.1. Simufilam's mechanism of action

Cassava Sciences' simufilam purportedly works to stabilize misfolded filamin A in the cell. Filamin A is an actin-binding scaffolding protein in the intracellular space with several functions. There are several different actin-binding proteins that do exactly what the description says; they bind to actin, another protein that's very abundant inside of most cells. Scaffolding proteins are regulators of key signaling pathways that behave in several ways, the first of which is the most basic: (a) tethering signaling components, (b) localizing these components to specific areas of the cell, (c) regulating signal transduction by coordinating positive and negative feedback signals, and (d) insulating the correct signaling proteins from competing proteins. Filamin A is involved in several functions, including various cell functions. For example, it regulates immune cells and fibroblasts and contributes to inflammation and cirrhosis in NASH.

Simufilam's effect in Alzheimer's disease would lie in the inhibition of two faulty signaling pathways in the disease:

- From amyloid plaques outside the cell, to the a7 nicotinic acetylcholine receptor on the cell surface, activating ERK and JNK1 to hyperphosphorylate tau inside the cell; and

- From amyloid plaques outside the cell, to the CD14 receptor on the cell surface, to the TLR4 receptor, to the creation of hyperphosphorylated tau inside the cell.



Source: Cassava Sciences corporate presentation, accessed June 2023.

Cassava Sciences claims that simufilam does not interact directly with amyloid or remove it but rather indirectly interacts with it by preventing its aberrant signaling through the α7 nicotinic acetylcholine receptor or a7nAChR and TLR4. That double prevention is said to respectively lead to less tau hyperphosphorylation and a reduction of neuroinflammation. Cassava Sciences' science therefore relies on the existence of amyloid plaques; if there are not plaques, there would be no faulty signaling through the a7nAChR to hyperphosphorylated tau and through the TLR4 receptor to promote neuroinflammation.

Therefore, simufilam does not leave the existence of amyloid plaques unaffected. Although it does not remove them, it should modify their faulty signaling through misfolded filamin A.

7.2. Scientific background

Rather little is published about simufilam's mechanism of action or filamin A's involvement in Alzheimer's disease or neurodegenerative diseases in general. It is possible that at this stage, its mechanism of action is not yet fully understood.

The most recent article was published on June 8, 2023 and is entitled "Targeting α7 nicotinic acetylcholine receptors and their protein interactions in Alzheimer's disease drug development." The focus in that article is solely on the search for treatments for AD from the angle of the a7nAChR receptor, not the TLR4 receptor.

The a7nAChR receptor is an acetylcholine receptor. Acetylcholine is a neurotransmitter. Cholinergic receptors, which are divided into active nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs), are stimulated by acetylcholine and enable signal transduction in the nervous system.

As a reminder, the current symptomatic standard-of-care treatment for AD includes donepezil, galantamine and rivastigmine, which are cholinesterase inhibitors thought to enhance brain acetylcholine levels uptake in AD patients. Galantamine has been reported to inhibit Aβ1–42-induced neurotoxicity by enhancing α7nAChR expression.

It is established that in AD, faulty amyloid-β accumulation coincides with altered expression and function of nicotinic acetylcholine receptors, with amyloid plaques and mostly $A\beta_{1-42}$ binding to a7nAChR.

An independent team reported in 2022 that insoluble filamin A is associated with amyloid but not with tau pathology. The team also reported that filamin A levels are at their highest at the intermediate levels of Alzheimer's disease, which may be a hallmark of prodromal AD within the MCI spectrum. However, filamin A is not specifically associated with neurodegeneration and cognitive decline.

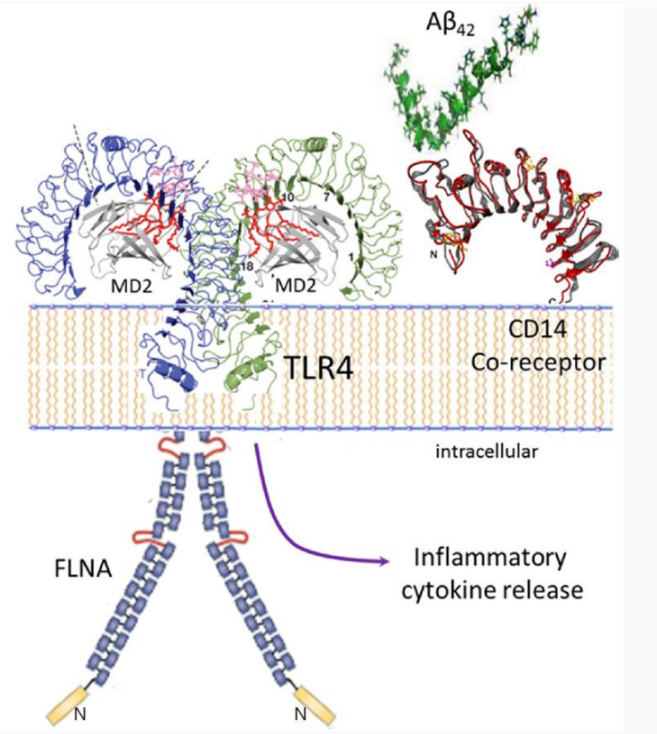
Another independent team reported a link between filamin A and tau pathology in the AD brain, finding that filamin A could contribute to tau pathology by altering tau protein levels and tau phosphorylation. It is not clear at this stage whether those findings require an interaction involving the a7nACh receptor.

Another independent study found that filamin A drove tau aggregation in progressive supranuclear palsy.

In Parkinson's disease, it has also been reported that oligomeric alpha-synuclein, the traditional hallmark of PD, interacts with TLR4 in macrophages to induce cytokine release, eliciting an immune response against alpha-synuclein oligomers and possibly an initiating role in PD pathogenesis.

7.3. Similarities and differences in mechanism of action

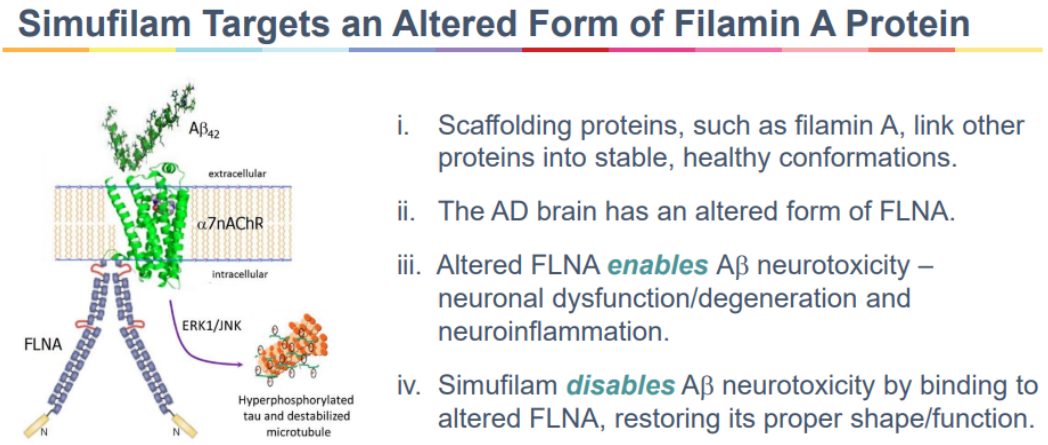
7.3.1. Anti-inflammatory activity through TLR4 and CD14



Source: L. Burns et al., Altered filamin A enables amyloid beta-induced tau hyperphosphorylation and neuroinflammation in Alzheimer's disease, Neuroimmunology and Neuroinflammation 4(12):263-71, December 2017

Simufilam is thought to work by inhibiting the inflammatory cytokine release that results from the altered conformation of filamin A through Aβ42. Cytokine release, mostly through the TLR4 receptor, is considered implicated in neurodegenerative diseases. Thus, inhibiting that pathway may reduce or inhibit inflammation.

7.3.2. Anti-inflammatory activity through inhibition of ERK1 and JNK

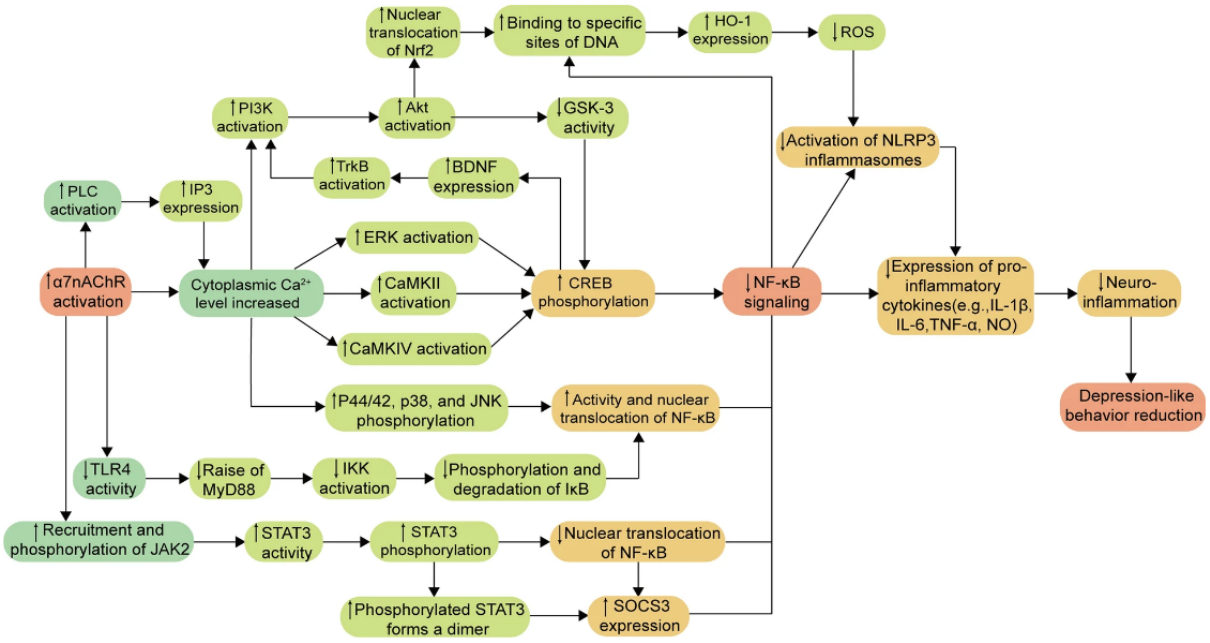


Source: corporate presentation Cassava Sciences, accessed June 2023

ERK and JNK kinases are reported to be activated to phosphorylate tau, as confirmed by other research. Simufilam may, therefore, (also) act as an anti-inflammatory treatment through inhibition of ERK1 and JNK. The cholinergic pathway used to reduce ERK1 and JNK signaling may be different than that used by NE3107 and/or XPro, however. In that regard, cholinergic treatments have been tested for Alzheimer's before, and many have been abandoned.

7.3.3. Possible anti-inflammatory activity through inhibition of NF-kB

Cassava Sciences has not reported any effect of simufilam on NF-kB signaling. Its selective inhibition of NF-kB can, however, not be excluded, as inhibition of ERK and JNK through the cholinergic pathway should lead to reduced NF-kB signaling and reduced expression of pro-inflammatory cytokines. The α7 nicotinic receptor, expressed in astrocytes and microglia, has been reported to be one of the main regulators of the "brain cholinergic anti-inflammatory pathway." It suppresses the synthesis of proinflammatory cytokines in macrophages and glial cells. The cholinergic activity also plays a role in modulating neuroinflammation in demyelinating diseases. It has been reported that α7 nAChR activation in astroglia blocked LPS-mediated NF-κB nuclear translocation, indicating that the observed anti-inflammatory effect may be mediated through inhibition of the NF-κB pathway.



Source: L. Zhao et al., α7 Nicotinic acetylcholine receptor: a key receptor in the cholinergic anti-inflammatory pathway exerting an antidepressant effect, Journal of Neuroinflammation, March 2023. Description of illustration: "*Molecular mechanisms of activation of α7 nAChR-mediated CAP. The activation of α7 nAChR could inhibit the expression of NF-κB through TLR4/NF-κB/NLRP3, JAK2/STAT3/NF-κB and Ca2+-related signaling pathways, reduce the production of inflammatory cytokines, reduce neuroinflammation, and finally play an antidepressant role. ↑: upregulate, ↓: downregulate, TLR4 Toll-like receptors 4, MyD88 myeloid differentiation factor 88, IKK inhibitor of kappa B kinase, IκB inhibitor of NF-κB, JAK2 Janus Kinase 2, STAT3 signal transduction and transcription activator 3, SOCS3 suppressor of cytokine signaling 3, NF-κB nuclear factors-kappa B, PLC phospholipase C, IP3 inositol 1,4,5-triphosphate, PI3K phosphatidylinositol 3-kinase, Akt protein kinase B, GSK-3 glycogen synthase kinase 3, BDNF brain-derived neurotrophic factor, TrkB tropomyosin receptor kinase B, ERK extracellular signal-regulated kinase, CaMKII Ca2+/calmodulin-dependent protein kinase II, CaMKIV Ca2+/calmodulin-dependent protein kinase IV, JNK c-Jun N-terminal kinase, Nrf2 nuclear transcription factor E2-related factor, HO-1 heme oxygenase-1, ROS reactive oxygen species, CREB cAMP-response element binding protein, NLRP3 NOD-like receptor protein 3, IL-1β interleukin-1β, IL-6 interleukin-6, TNF-α tumor necrosis factor-α, NO nitric oxide*"

It has also been reported that a7nAChR activation reduces inflammatory responses in a rat model of Parkinson's disease,

The pathway used to reduce NF-kB signaling may be different, however. In that regard, cholinergic treatments have been tested for Alzheimer's before, and, as stated earlier, many have been abandoned.

7.3.4. Improved insulin receptor signaling involving IRS1

Insulin receptor substrate 1 (IRS1), shown in green in four places in the illustration below, plays a key role in transmitting signals from the insulin and insulin-like growth factor-1 receptors to others along the ERK kinase pathway. ("*Enabled by altered FLNA's new linkages, Aβ42 activates α7nAChR to hyperphosphorylated tau and contributes to insulin receptor desensitization. Although the insulin receptor is constitutively associated with native FLNA, it is possible that altered FLNA also contributes to the insulin receptor dysfunction in AD.*")

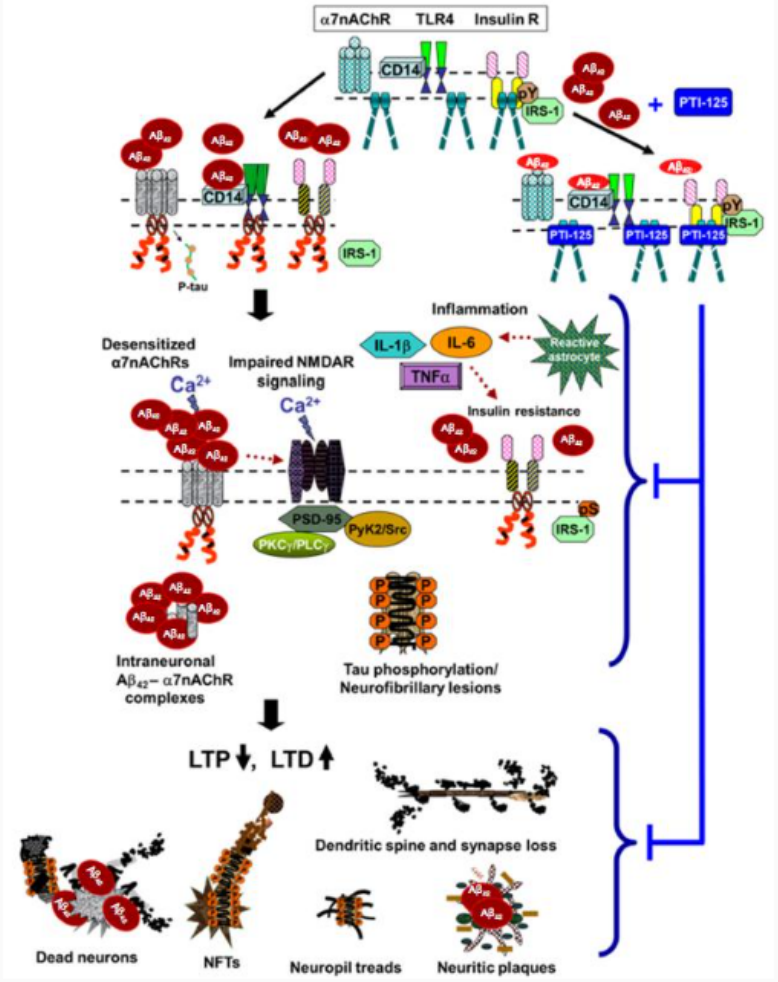


Figure 3. Proposed model of pathological consequences of altered FLNA-enabled $A\beta_{42}$ signaling via α7nAChR and TLR4. Soluble $A\beta_{42}$ monomers or small oligomers bind α7nAChR or CD14, complexed with TLR4, inducing recruitment of FLNA to these receptors. Dimers of native FLNA, coupled to insulin receptors but not to α7nAChR or TLR4, are depicted as straight rods; red curly FLNA depicts the altered form, which is recruited to α7nAChR and TLR4 (and possibly also insulin receptors). Enabled by altered FLNA's new linkages, $A\beta_{42}$ activates α7nAChR to hyperphosphorylate tau and persistently activates TLR4 to induce inflammatory cytokine release (TNFα, IL-1β and IL-6) by reactive astrocytes. This neuroinflammation likely contributes to insulin receptor desensitization[57]. Although the insulin receptor is constitutively associated with native FLNA, it is possible that altered FLNA also contributes to the insulin receptor dysfunction in AD. $A\beta_{42}$'s aberrant signaling through α7nAChR impairs function of α7nAChR and of NMDARs, restricting calcium influx through both receptors. Increasing $A\beta_{42}$ piling onto α7nAChR leads to intraneuronal $A\beta_{42}$-α7nAChR complexes. The hyperphosphorylated tau dissociates from microtubules, disrupting microtubule stability, axonal transport and neuronal function. Along with dysfunctional tau, impaired NMDARs reduce LTP and heighten LTD. Dendritic spines and synapses are lost. Neuritic plaques, neuropil treads and neurofibrillary tangles are formed, and neurons degenerate. FLNA: filamin A; Aβ: amyloid beta; α7nAChR: α7 nicotinic acetylcholine receptor; TLR4: toll-like-receptor 4; TNFα: tumor necrosis factor-α; IL: interleukin; AD: Alzheimer's disease; NMDAR: N-methyl-D-aspartate receptor; LTP: long-term potentiation; LTD: long-term depression

Source: L. Burns et al., Altered filamin A enables amyloid beta-induced tau hyperphosphorylation and neuroinflammation in Alzheimer's disease, Neuroimmunology and Neuroinflammation 4(12):263-71, December 2017

A group including Cassava Sciences' Lindsay Burns reported in 2012 that both tau phosphorylation and activation of TLR4 through Aβ42 required filamin A. Among other pathways, one sees (in the top and middle of the picture above, how reactive astrocytes drive inflammation, including cytokines TNF, IL-1B and IL-6, eventually leading to insulin resistance, which simufilam (PTI-125) purportedly corrects.

In preclinical models, simufilam had been seen to reduce tau hyperphosphorylation and neuroinflammation and improve function of the α7nAChR, NMDAR and insulin receptors.

"*The improved insulin receptor signaling may also reflect reduced neuroinflammation, as neuroinflammation has been linked to impaired insulin receptor function. Disrupting the FLNA-TLR4 linkage, PTI-125 potently and efficaciously reduced inflammatory cytokines by at least 80% in 3xTg AD mice and in ICV Aβ42-infused mice. Correlating with the improved NMDAR function, synaptic plasticity was also improved* […]"

On June 27, 2023, Cassava Sciences reported that simufilam suppresses overactive mTOR and restores its sensitivity to insulin in the lymphocytes of Alzheimer's patients.

7.3.5. Biomarkers

The biomarkers reported by Cassava Sciences at six months of treatment show, among other effects, a strong decrease in tau levels and markers of glial activity and neurodegeneration.

Total tau decreased by 38%, and total p-tau181 decreased by 18%. The neurodegenerative markers neurogranin and neurofilament light decreased by 72% and 55%, respectively, in the Cerebrospinal fluid (CSF). The change in NfL levels is most important here as it may, at some point, become a surrogate endpoint in Alzheimer's and, possibly, other neurodegenerative diseases, with Biogen's Qualsody (tofersen) as precedent. The inflammatory marker YKL-40 was decreased by 44%, while the microglial activity marker sTREM2 was decreased by 65%.

Simufilam's 28-day placebo-controlled, biomarker-focused trial in 64 patients on 50mg and 100mg doses changed several biomarkers by statistically significant values, many of which were correlated to dosage, such as T-tau (-15%/-18%), P-tau (-8%/11%), Aβ42 (+17%/+14%), Ng (-36%/-43%), NfL (-28%/-34%), IL-6 (-10%/-11%), YKL-40 (-10/-12%), and sTREM2 (-42/-46%).

7.3.6. Potential to stabilize cognitive decline, excluding moderate patient population

7.3.6.1. Earlier data

Simufilam's 28-day trial also showed improved cognition compared to placebo as evaluated with the Cambridge Neuropsychological Test Automated Battery (CANTAB), but that result was not statistically significant. Effect sizes were 46% to 17% versus placebo. Episodic memory for the 50 mg and 100 mg drug group improved by -5.7 and -4.3, respectively, with lower scores being better, versus -1.5 for patients on placebo. Spatial memory for the 50 mg and 100 mg drug group improved by -1.6 and -3.3, respectively, versus -0.4 for placebo patients.

Simufilam's final open-label results in 200 patients on the ADAS-Cog rating scale showed that cognition worsened by 0.5 point. Historical data show an average decline of six to 12 points. Patients with less-progressed disease improved by 2.4 points, whereas those with further-progressed disease worsened by 4.4 points. As a reminder, Cassava Sciences had reported an average improvement of 1.6 points in 50 patients at six months, 3.0 points at nine months, and 3.2 points at 12 months. However, for the first 100 patients, that number dropped to 1.5 points over 12 months, suggesting that the cognition of patients 51 to 100 did not improve but still stabilized over the course of 12 months.

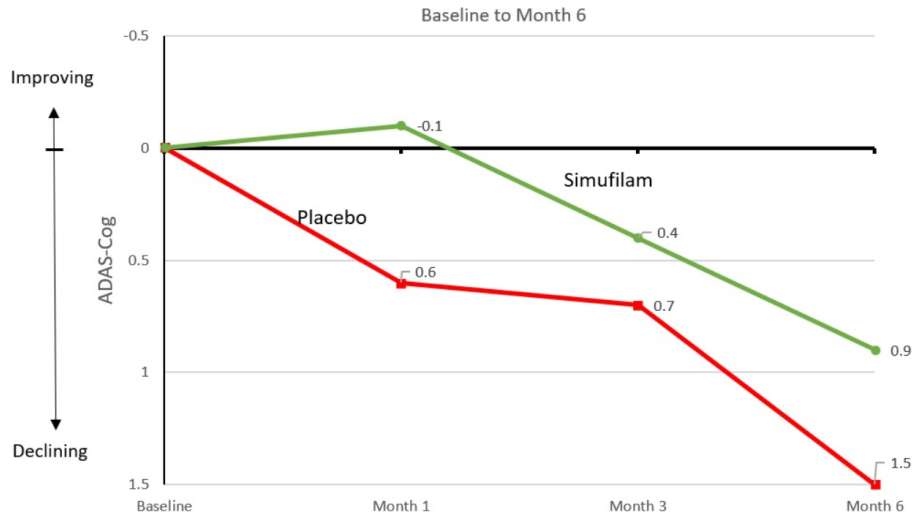
7.3.6.2. The moderate patient population could be a significant risk factor

Simufilam's placebo-controlled Cognition Maintenance Study followed those patients for another six months, wrapping up after one year. Half of the patients were on placebo, the other half continued to

take simufilam. On July 5, 2023, Cassava Sciences reported that simufilam slowed cognitive decline by 38% versus placebo.

Full Analysis Set	**Drug (N = 78)**	**Placebo (N = 77)**
6-month Change in ADAS-Cog	- 0.9 point Decline	- 1.5 point Decline

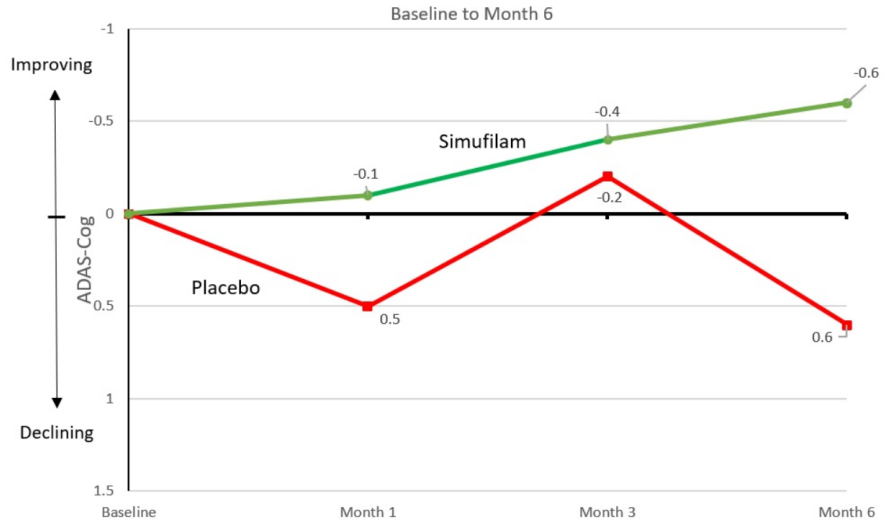
Source: Cassava Sciences press release of July 5, 2023.



Source: Cassava Sciences press release of July 5, 2023.

Mild Patients	**Drug (N= 40)**	**Placebo (N= 36)**
6-month Change in ADAS-Cog	0.6 point Improvement	- 0.6 point Decline

Source: Cassava Sciences press release of July 5, 2023.



Source: Cassava Sciences press release of July 5, 2023.

Remarkably, simufilam performed much better during the study at improving patients' cognition in the population with mild Alzheimer's disease than in the population with moderate Alzheimer's.

However, the results were not statistically significant, which is important to note given the fact that this study was placebo-controlled. It means these highly variable results could merely be due to chance.

No data have been given for patients in the moderate group, either on placebo or on the drug. By the author's estimates, the data for the groups with moderate Alzheimer's disease could be the following, although these are only estimates and indicative.

Moderate Patients	**Drug (N= 38)**	**Placebo (N= 41)**
6-month Change in ADAS-Cog	- 2.5 point decline	- 2.3 point decline

Source: own work.

If these numbers are correct, then the patients with moderate Alzheimer's disease on placebo declined less than those with moderate Alzheimer's on the drug. That would put any trial of Cassava Sciences in patients with moderate Alzheimer's disease at severe risk of failure.

7.3.7. Responder heterogeneity

The cognitive scoring over one year in 200 patients suggests that there is heterogeneity in the treatment response by patients.

7.3.8. Systemic normalization / anti-aging

On June 27, 2023, Cassava Sciences reported that by suppressing an overactive mTOR, simufilam restored insulin sensitivity. mTORC1 activation contributes to aging in several different ways, such as through acceleration protein synthesis, mitochondrial energy production, oxidative stress and cellular senescence. Additionally, mTORC1 itself contributes to aging by actively suppressing autophagy. Further, in addition to promoting aging, overactivation of mTORC1 appears to contribute to AD. This overactive mTORC1 signaling in AD appears related to soluble amyloid β1-42 (Aβ42) because Aβ42 activates the PI3K/Akt pathway, leading to mTORC1 activation.

Simufilam restored insulin sensitivity by, among other ways, reducing basal mTORC1 and mTORC2 signaling and basal Akt1 activation. As mentioned above, as diabetes and insulin resistance can be considered to be heavily implicated in the disease, this is important news.

7.3.9. Safety

Simufilam appears to have a seemingly safe profile, and no serious side effects have been reported so far.

7.3.10. Fast onset

Simufilam seems to have a fast onset compared to anti-amyloid therapies.

7.3.11. No infusion

Simufilam can be taken in the form of a pill.

7.3.12. Dual mechanism of action

Simufilam is reported to modify Alzheimer's disease both by reducing tau phosphorylation and by lowering chronic neuroinflammation. As Alzheimer's is multifactorial, a dual mechanism may be of value here.

8. Coya Therapeutics

8.1. Coya 301's mechanism of action

It has been suggested on several occasions that activation of regulatory T cells (Tregs), also cellular regulators of inflammation, may have immune-rebalancing and therapeutic benefits in several indications, including autoimmune diseases.

Coya Therapeutics is pursuing that route through administration of low-dose IL-2 alone (Coya 301) or in combination with a macrophage depletor (Coya 302). The results reported so far from two open-label studies are:

- Stabilization of cognition and lowering of inflammatory cytokines and chemokines in Alzheimer's disease with Coya 301, i.e., low-dose IL-2 to promote Treg activation;
- Stabilization of disease progression in ALS with Coya 302, i.e., low-dose IL-2 in combination with a macrophage depletor.

Coya is pursuing a treatment for ALS first and plans to define a further strategy for AD after having received top-line data in Q2 2024 from an ongoing academic Phase 2 double-blind randomized trial (supported by the Gates Foundation and Alzheimer's Association) in up to 46 mild-to-moderate AD patients.

8.2. Scientific background

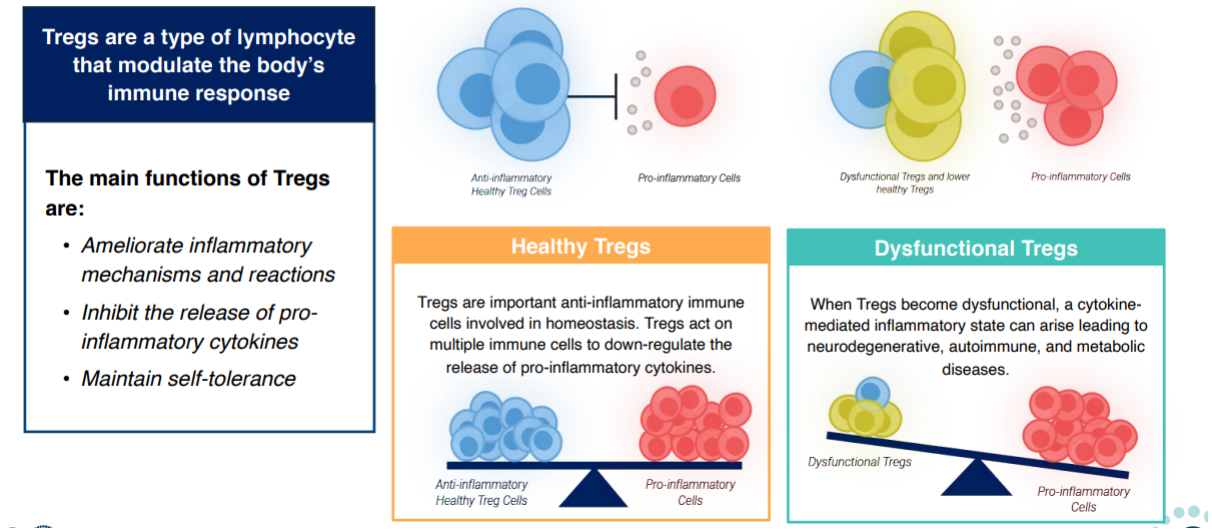
Regulatory T cells are a subset of T cells that are immunosuppressive and express CD4, FOXP3 and CD25. Their function is to inhibit and terminate immune reactions and maintain immune balance. Their pro-inflammatory counterparts are effector T cells.

It has been suggested on several occasions that activation of Tregs, which are also cellular regulators of inflammation through agonism of the TNFR2, may have immune-rebalancing and therapeutic benefits in several indications, including autoimmune diseases.

Tregs have been established as dysfunctional in neurodegenerative diseases[27]. Coya's approach is not about inhibiting a proinflammatory pathway or protein outside the cell but rather, to promote the activity of one specific type of immune cells that's considered of primordial influence in the regulation of inflammation. Coya stimulates Tregs with low-dose IL-2.

[27] The scientific team behind Coya has shown this on several occasions. An external team has recently shown success with autologous Treg therapy in a Parkinson's model.

What Are Tregs and How They Are Dysfunctional



Source: Coya corporate presentation, accessed June 2023.

8.3. Similarities and differences in mechanism of action

Coya takes a different approach to rebalancing the immune system and allowing for homeostasis, namely, by modulating Tregs (and depleting macrophages, in the case of Coya 302). Therefore, a pathway analysis similar to that made with regards to Cassava Sciences, BioVie and INmune Bio cannot be made. However, in terms of the rationale and efficacy, a comparison can be made.

8.3.1. Anti-inflammatory activity through the modulation of Tregs

Coya has reported selective expansion of the Treg population after administration of its treatment candidate Coya 301. In fact, the mean percentage of Tregs almost doubled by the end of the treatment, with mean Treg suppressive function going from 46.61% at baseline to 79.5% at the end of treatment (p=0.003).

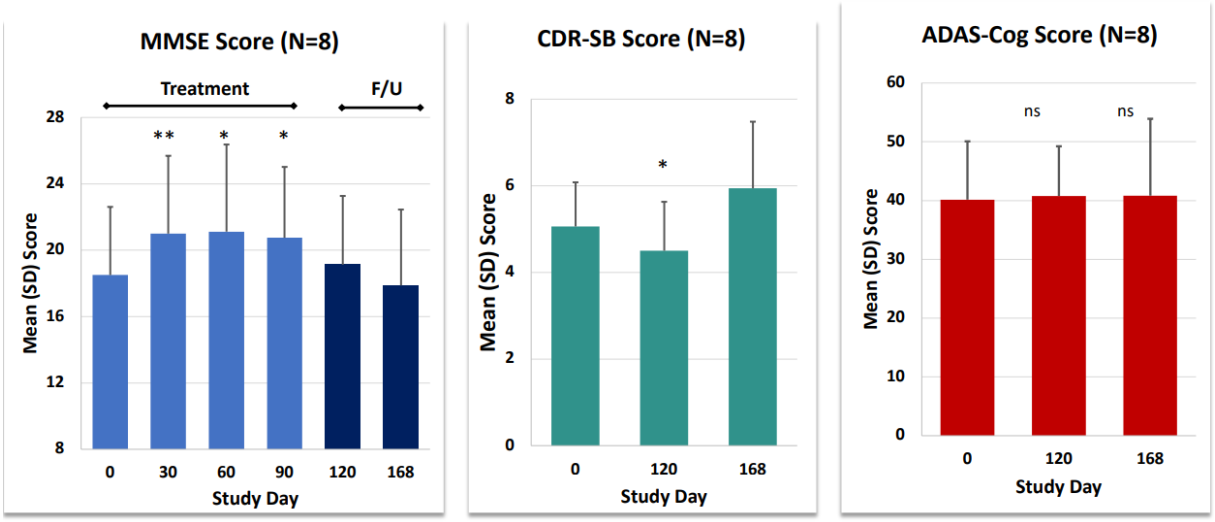
The effect of merely modulating Tregs, as reported by Coya with Coya 301, is that major inflammatory cytokines are also reduced.

Both BioVie and INmune Bio have reported similar correlations. Systemic TNF is associated with more rapid cognitive decline in Alzheimer's patients. Coya has also reported enhanced Treg function and numbers and reductions in other proinflammatory cytokines, such as CCL11, CCL2 and IL-15, after treatment of patients with AD.

8.3.2. Potential to stabilize cognitive decline

Coya has reported stabilization of cognition in Alzheimer's patients in a small open-label study. In eight patients treated over a four-month treatment period, Coya reported a statistically significant improvement in cognitive function as measured on the MMSE rating scale and no cognitive decline as measured on the ADAS-Cog and CDR-SB rating scales.

COYA 301 Improved or Halted Cognitive Decline in AD Patients



*p<0.05, **p<0.01 ns: not significant

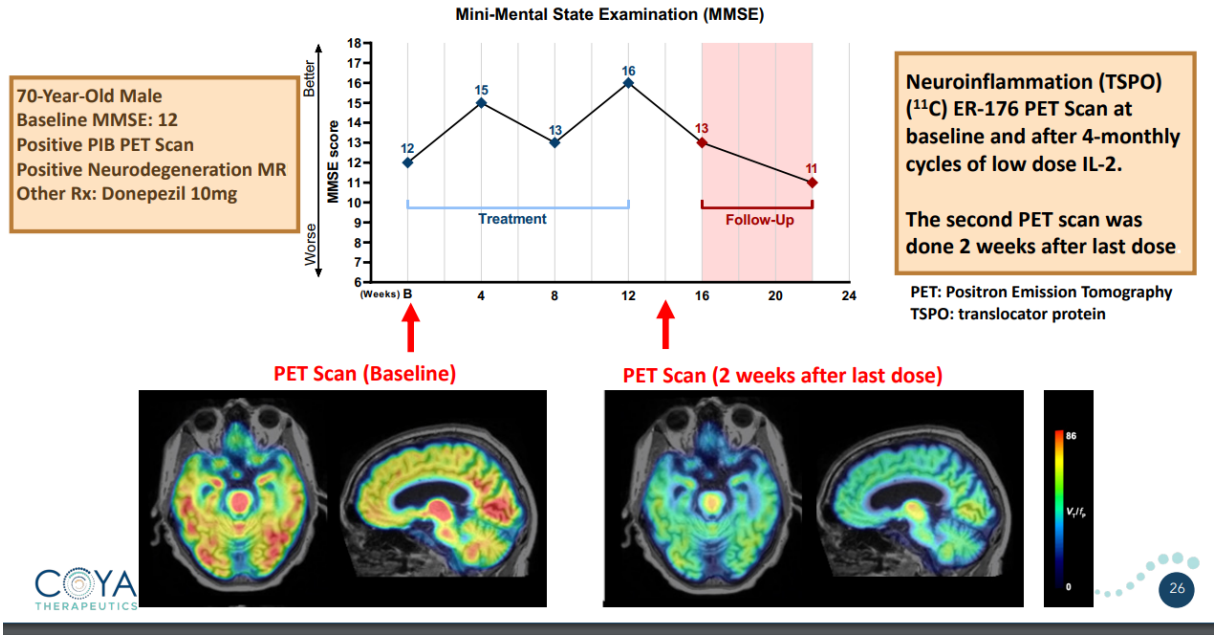
COYA THERAPEUTICS

MMSE: Mini-Mental State Examination, ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale
CDR-SB: Clinical Dementia Rating scale – Sum of Boxes

22

Source: Coya corporate presentation, accessed June 2023.

Case Study of Brain Imaging of AD Patient before and after COYA 301 treatment



COYA THERAPEUTICS

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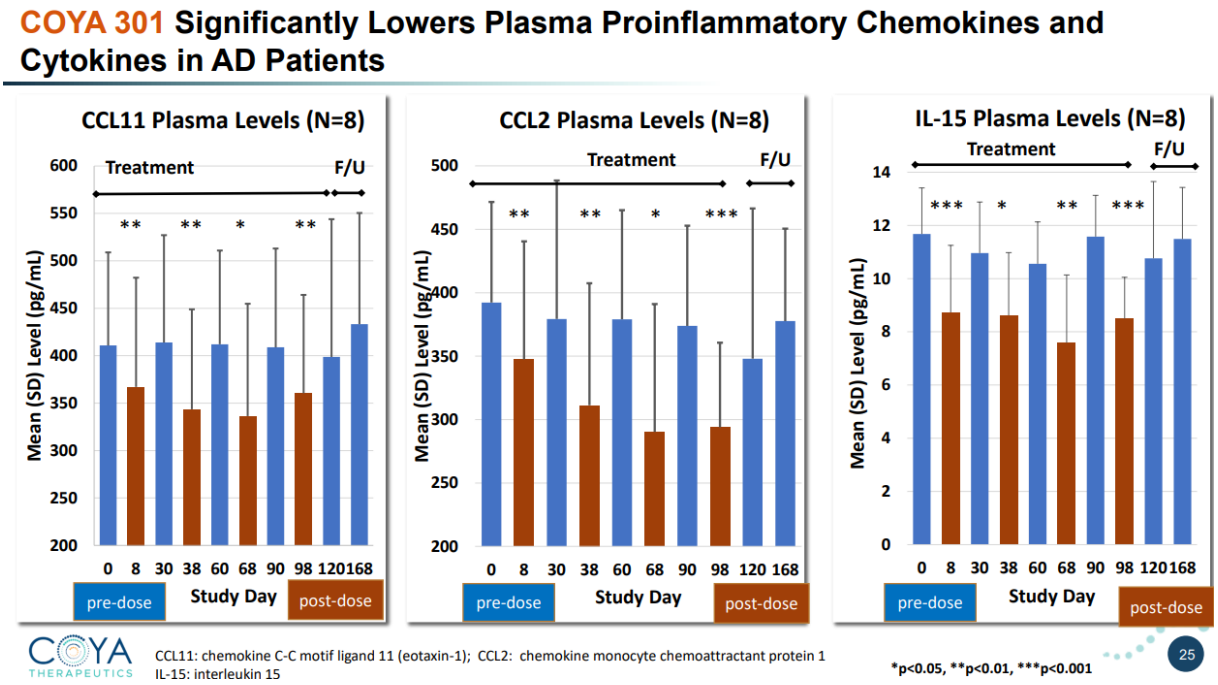
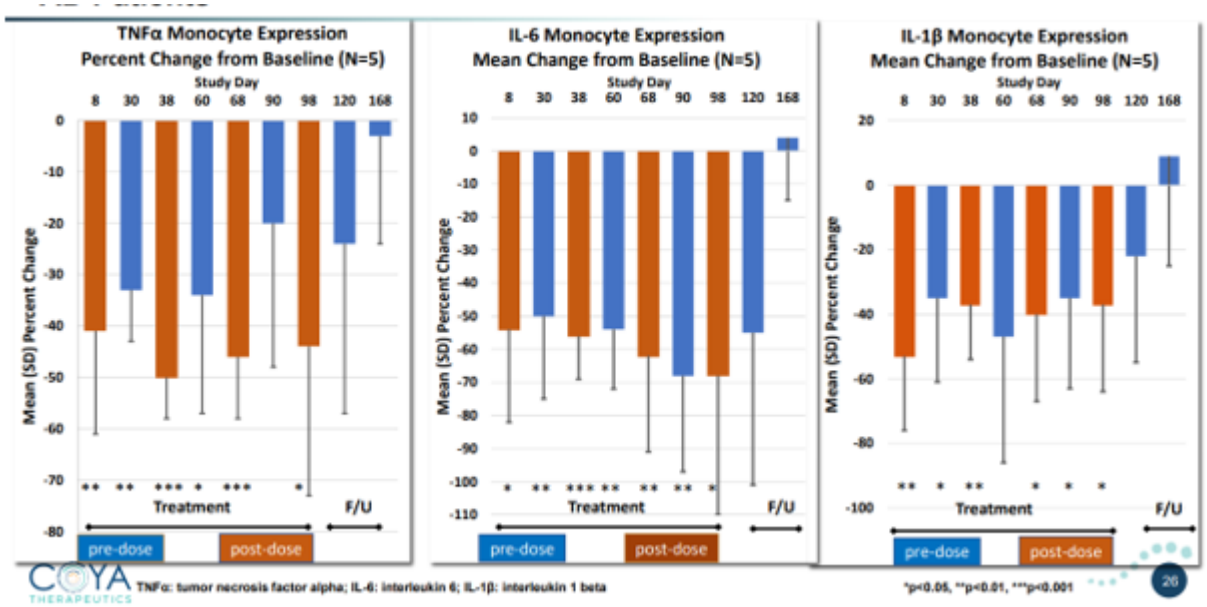
Source: Coya corporate presentation, accessed June 2023.

8.3.3. Biomarkers

Coya has reported a significant reduction in several proinflammatory cytokines and chemokines, including TNF, IL-6 and IL-1B.



Source: Coya Therapeutics corporate presentation



Source: Coya Therapeutics corporate presentation

Further reporting showed reduction of CCL4 and FLT3LG.

8.3.4. Treg differentiation through TNFR2 stimulation, a7nAChR stimulation and ERK-JNK involvement

Coya stimulates Tregs with low-dose IL-2. However, there are other ways to do it that follow similar pathways to those reported above and are hence worthwhile mentioning here.

As TNFR1 primarily mediates inflammation and apoptosis and activation of TNFR2 mainly promotes cell proliferation and survival, scientists have considered TNFR2 agonism to promote Treg activation. A TNFR-2 selective agonist has been reported to rescue human neurons from oxidative stress-induced cell death.

In that regard, it has also been reported that a7-nicotinic receptor agonism, which led to neuroprotective effects in a Parkinson's rat model, was found to have a greater increase in the expression of regulatory T cells compared to the lesion group, which revealed that the neuroprotective effect of a7nAChR activation might be partially due to Treg differentiation. The ERk and JNK pathways are also involved in adaptive Treg differentiation.

8.3.5. Safety

Coya 301 and Coya 302 appear to have safe profiles, and no serious side effects have been reported so far.

8.3.6. Fast onset

Coya 301 and Coya 302 seem to have a fast onset compared to anti-amyloid therapies.

9. Risks

9.1. General

The above report sets out similarities between the mechanisms of action of different drug candidates from different companies. Investing in any of these companies entails several risks, some of which will be mentioned here.

Each of these companies is managed by different people and may be at a different stage of development and facing different hurdles. Each of these drug candidates have several differences which may affect efficacy, treatment response, and symptomatic vs. disease-modifying effects. Trials may be halted or abandoned at any stage. Management may also need to obtain further financing, diluting shareholders.

Furthermore, as Alzheimer's is a multifactorial disease, it is likely that one treatment will not be a fit for all patients. Amyloid aggregation is not specific to Alzheimer's disease. It is also seen in other bodily diseases and in Parkinson's disease. About 30% of older adults also have amyloid aggregation but do not go on to develop Alzheimer's disease. Conversely, although Alzheimer's is the most common form of dementia, several other forms of dementia exist that do not involve amyloid aggregates as the typical hallmark. Neurofibrillary tau tangles also aren't exclusive to Alzheimer's disease. There are other different tauopathies.

Some of these companies also have other drug candidates or may target different indications. Cassava Sciences is the exception here.

9.2. Risks for NE3107 and BioVie

We highlight five possible risks with regards to NE3107 and BioVie:

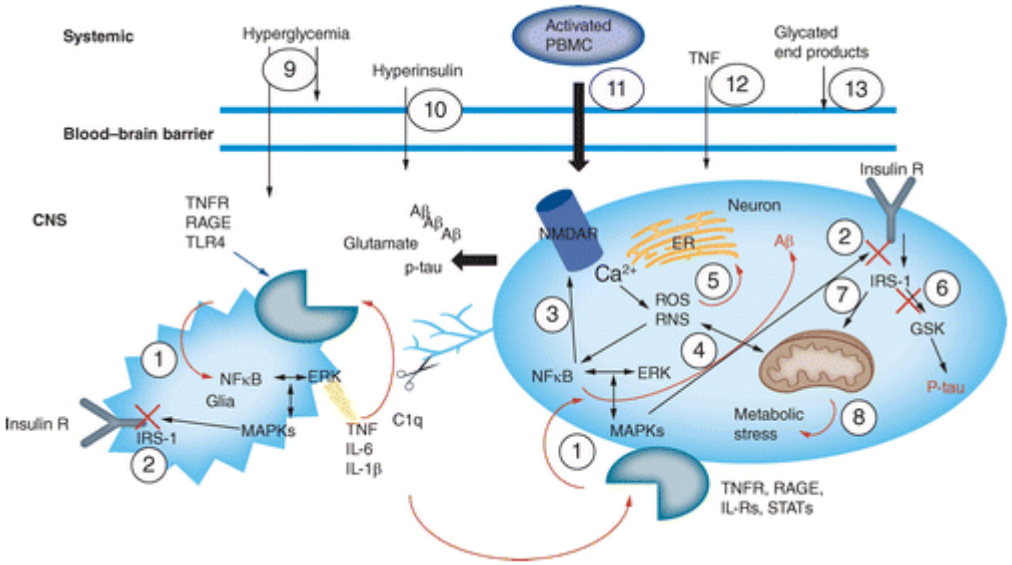
- NE3107 may not be sufficiently selective;
- Pathway circumvention over time;
- Possible divergence in treatment response between the mild and moderate AD populations;
- The risk of inhibiting TNF entirely;
- Trial design risks.

9.2.1. Lack of substantial evidence of selectivity and homeostasis

NE3107 has been tested abundantly in other indications, and hence, there is a breadth of scientific articles available on this drug candidate. An essential part of BioVie's thesis lies in the selectivity of NE3107 and its promotion of homeostasis. The abstract to BioVie's published rationale for a Phase 3 design mentions that NE3107 has been shown to selectively inhibit inflammation-driven ERK- and NF-κB-stimulated inflammatory mediators, including TNF-α, without inhibiting their homeostatic functions. The rationale itself contains further detail and several references to scientific publications.

Insofar as we understand it, NE3107's selectivity would lie in the combination of decreased inflammatory signaling through reduced ERK signaling with improved ERK-dependent insulin signaling, without the inhibition of homeostatic functions. This includes, among other effects, the reduction of toxic Aβ production through reduced inflammation, reduced Aβ aggregation through

reduced oxidative stress, and reduced P-tau production through the restoration of insulin-signaling regulation.



Source: M.F. Murphy et al., NM101 Phase III study of NE3107 in Alzheimer's disease: rationale, design and therapeutic modulation of neuroinflammation and insulin resistance, Future Medicine, July 2021.

The reduction of inflammation should lead to reduced activation of microglia, which should drive homeostasis.

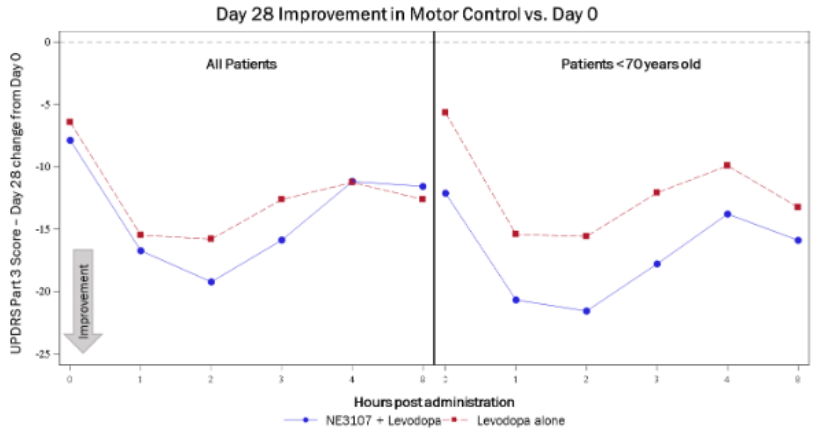
However, as we understand it, the decrease of systemic TNF impact on brain inflammation relates to the production of both transmembrane and soluble TNF, whereas transmembrane TNF may be beneficial to the production of the myelin sheath and remyelination.

It is therefore unclear whether the mentioned selectivity and homeostasis will be relevant to BioVie's long-term disease-modifying ambitions with NE3107.

9.2.2. Divergence in treatment response between mild and moderate AD populations

BioVie's results from its investigator-initiated open-label study in Alzheimer's show a divergence in treatment response between patients with baseline scores of more than 20 on the MMSE scale versus those with scores of less than 20.

Furthermore, BioVie has reported good results from a 28-day placebo-controlled trial in Parkinson's, which indicated that younger patients (<70 years old) had better treatment responses.



There appears to be a divergence between treatment populations, which BioVie links to less progression of disease and – in the case of Parkinson's – more remaining dopamine and dopaminergic neurons. It is possible that the same or an even stronger divergence could be seen in placebo-controlled trials, which may place these trials at risk of achieving statistical significance.

As Alzheimer's is considered a multifactorial disease, it is possible that NE3107 could have limited or no effect in certain subpopulations. BioVie has not proven that ERK- and NF-kB-related inflammation is the cause of Alzheimer's in all patients with the disease.

9.2.3. Pathway circumvention or receptor overstimulation over time

An effect seen with many drugs is that over time, efficacy wears off due. This may be due to overstimulation of receptors or circumvention of pathways. Therefore, long-term efficacy data is important. Historically, TNF inhibitors continue to be efficacious over time, which may indicate low risk here for BioVie, although the mechanism of action of traditional TNF inhibitors is different.

9.2.4. The risk of inhibiting TNF entirely

Traditional TNF inhibitors come with a serious risk of side effects in case of long-term use, such as improper defense against pathogens. BioVie has shared data on the reduction of TNF, but not more specifically as to which type of TNF or the exact percentage of reduction. Inhibition of inflammation should not unselectively lead to the entire reduction of any inflammation unrelated to the disease itself, such as amyloid plaques and neurofibrillary tangles, as this may prevent the homeostatic and normal phagocytic and nurturing functions of glial cells.

Then again, taking into account the long duration before the onset of symptoms, the multitude of metadata-based publications showing the benefit of traditional, non-brain-penetrant TNF-inhibitors in the prevention of Alzheimer's may indicate that broad TNF inhibition may be efficacious as well.

9.2.5. Trial design risks

BioVie has one six-month Phase 3 trial ongoing in mild-to-moderate Alzheimer's disease, which is slated for a topline readout in Q4 2023.

The above results have shown that there appears to be a wide divergence between treatment populations, the reason for which at this point is unknown. As Alzheimer's is considered a multifactorial disease, it is possible that NE3107 will have little to no effect in certain subpopulations. NE3107 targets inflammation and insulin resistance, although patients at first glance do not appear to have been recruited on this basis.

However, the baseline CRP data of the patients in BioVie's Phase 3 trial may indicate that patients enrolled in this trial have a considerable level of inflammation, on average.

Table 1. Baseline Characteristics

Characteristic	All N=378	Aβ+ [a] n=57	Aβ− [b] n=77	P	*APOE* ε4+ n=97	*APOE* ε4− n=259	P
Age, mean (SE) y	73 (0.3)	76 (0.8)	72 (0.6)	**	73 (0.6)	73 (0.4)	-
Female, %	55	53	67	-	64	64	-
High WHR [c], %	85	84	84	-	81	82	-
FPG, mean, mg/dL	112	100	112	*	106	115	*
IFG, %	32	18	35	#	25	36	-
T2D, %	20	14	22	-	17	25	
Fasting insulin, mean (SE), µlU/mL	16 (1.1)	10 (1.0)	15 (2.4)	*	12 (1.1)	17 (1.6)	*
High (>23), %	15	9	15	-	10	17	-
HOMA2-IR, mean (SE)	1.8 (0.1)	1.3 (0.2)	1.9 (0.2)	*	1.5 (0.1)	1.9 (0.1)	*
1.4-2.5, %	27	13	29	##	24	27	-
>2.5, %	20	15	21	-	15	22	-
MAGE, mean (SE), mg/dL	70 (2.5)	62 (3.4)	68 (4.6)	-	68 (4.2)	71 (3.1)	-
CRP, mean (SE), mg/L	4.1 (0.4)	1.8 (0.2)	6.3 (1.2)	**	3.6 (0.8)	4.3 (0.4)	
>3, %	67	13	28	#	20	32	-
>10, %	18	0	18	##	4	21	

CRP is a measure of inflammation also used by INmune Bio. As one is targeting chronic inflammation, the traditional value of a CRP of >3 to measure acute inflammation is not relevant. Thus, a much lower value (e.g., half of the value for acute inflammation) should be relevant. At baseline, 67% of the patients in BioVie's Phase 3 trial had a CRP value of above 3. This has the author assume that patients who entered this trial have high chances of responding to an anti-inflammatory treatment. Therefore, the above baseline data may be considered as de-risking BioVie's Phase 3 trial.

Traditional cognitive rating scales, including the CDR-SB, ADAS-Cog12, ADCS-CGIC, ADCS-ADL, MMSE and NPI-12, are used by BioVie as primary and secondary endpoints and could show a ceiling effect in some patients. Therefore, the trial results may not fully represent every cognitive change in every patient, which may lead to reduced changes in efficacy and statistical significance. The number of cognitive tests being undertaken could reduce the chances of the trial being a failure through consistency of results.

It is generally known that less efficacy is seen in patients with more-advanced disease. BioVie's Phase 3 trial aims to treat patients with both mild and moderate Alzheimer's disease. The baseline data of the patients in BioVie's Phase 3 trial, as reported on June 26, 2023, showed that the mean MMSE score was 20. That places those patients in the middle between mild and moderate Alzheimer's disease (mild Alzheimer's disease: MMSE 21–26, moderate Alzheimer's disease: MMSE 10–20, moderately severe Alzheimer's disease: MMSE 10–14, severe Alzheimer's disease: MMSE less than 10). For reference, Eisai's Phase 3 trial of lecanemab (Leqembi) had the majority of patients with mild cognitive impairment and about one-third of them with mild Alzheimer's disease, with a mean MMSE score of 25.

Finally, a trial with a duration of six months may not be considered long enough to allow a decision by a regulatory authority as to whether the drug candidate has disease-modifying potential. All of BioVie's studies, however, do have open-label extension studies which could be taken into account in that respect.

9.2.6. Two treatment candidates and four targeted indications

BioVie has two treatment candidates in its pipeline, namely, NE3107 for neurodegenerative diseases and continuous terlipressin.

With NE3107, BioVie aims to bring solutions to the unmet medical needs in three indications, namely, AD, mild cognitive impairment (MCI) and PD.

With continuous terlipressin, BioVie aims to bring solutions to the unmet medical need in refractory ascites. Although this asset is substantially de-risked and in a far-advanced stage of trial, continuous terlipressin does not seem to receive a lot of attention from investors.

Any negative/positive reporting on NE3107 may impact the assessment of trial success in both neurodegenerative indications but should leave the assessment of success of continuous terlipressin in refractory ascites unaffected.

9.3. Risks for XPro and INmune Bio

We highlight four possible risks with regards to XPro and INmune Bio:

- Litigational/regulatory;
- Pathway circumvention over time;
- The involvement of another trial for FTD and INKmune for high-risk MDS/AML;
- INmune Bio is in an earlier stage in AD.

Contrary to the companies and drug candidates mentioned above, INmune Bio's website features 81 preclinical scientific publications on XPro, many of which originate from outside laboratories and scientists.

These publications, taken together with the Phase 1 results, show the disease-modifying potential of XPro with biomarker results from a Phase 1 study that could keep on improving over a 12-month timeframe.

Targeting only soluble TNF to reduce inflammation, thereby allowing homeostasis and remyelination and possibly preventing the side effects seen with other TNF inhibitors, appears to be a very focused approach.

By only allowing on patients with sufficiently high levels of inflammation whose biology matches the MoA of XPro, INmune Bio has a selective trial design which may raise the chances of a successful topline readout and statistical significance.

Finally, trial design risk may be further reduced by using the novel, allegedly very-specific cognitive endpoint EMACC. Further endpoints are CDR, E-Cog, ADCS-ADL and NPI.

9.3.1. Litigational/regulatory risks

INmune Bio initiated a Phase 2 trial in 201 participants with Alzheimer's disease in the first part of 2022. That trial has been recruiting patients in Australia since its initiation in February 2022.

INmune Bio received a clinical hold letter from the FDA in May 2022 related to manufacturing issues. Shareholders of INmune Bio were informed about the content of this hold letter after INmune Bio first received it. However, on its more recent quarterly earnings calls, INmune Bio has not been open about the exact content of the follow-up correspondence exchanged with the FDA and the meeting it had with the FDA.

In any case, INmune Bio now appears to believe the clinical hold will be lifted by the fourth quarter of 2024. It is possible that INmune Bio will be required to produce a new batch of XPro according to the standards requested by the FDA, with the ensuing cost and potential delay, or that the FDA will have other requests.

Although a successful placebo-controlled Phase 2 trial does not necessarily need to include U.S. citizens, it may be preferable that the drug administered to patients in this trial does not face criticism from any regulatory authority.

INmune Bio has announced that it will update its investors when the trial is half-enrolled. Such an announcement has yet been made.

9.3.2. Pathway circumvention or receptor overstimulation over time

An effect seen with many drugs is that over time, efficacy wears off. This may be due to overstimulation of receptors or circumvention of pathways. Therefore, long-term efficacy data is important. Historically, TNF inhibitors continue to be efficacious over time, which may indicate low risk here for INmune Bio. Additionally, 12-month biomarkers reported by INmune Bio from its Phase 1 study show continuing and improving efficacy over a 12-month period.

9.3.3. Two treatment candidates and several targeted indications

INmune Bio has two treatment candidates in its pipeline, namely, XPro for neurodegenerative diseases and INKmune for the treatment of cancers.

With XPro, INmune Bio efforts to bring solutions to the unmet medical needs in two indications, namely, AD and treatment-resistant depression (TRD). The market for treatment-resistant depression is valued at 1.9 billion, and the market for major depressive disorder is 5.6 billion. Very few trials have been registered for anti-inflammatory treatments for this indication in spite of the strong scientific rationale. Development of new drugs for depression seems to be focused on improving existing therapies – which only work in about two-thirds of depressed patients – and (derivatives of) psychedelics.

With INKmune, INmune Bio aims to bring solutions to the unmet medical needs in high-risk myelodysplastic syndromes (MDS)/ acute myeloid leukemia (AML) and prostate cancer. Although not covered here, INKmune is a state-of-the-art treatment candidate targeting natural killer cells.

Any negative/positive reporting on XPro may impact the assessment of trial success in AD and TRD but should leave the assessment of success of INKmune in the targeted cancers unaffected. The same goes, *mutatis mutandis*, for reporting for INKmune.

9.3.4. INmune Bio is at an earlier stage in AD

INmune Bio has a history of constantly reorganizing its pipeline, either with regards to AD or XPro. XPro is in Phase 2 trials for AD, which makes its trajectory to approval longer and incurs a statistically higher risk of trial failure. It also means that the company is expected to require significant additional funding after the end of its Phase 2 trials, whether or not they lead to successful reporting.

9.4. Risks for simufilam and Cassava Sciences

We highlight six possible risks with regards to simufilam and Cassava Sciences:

- Lack of substantial scientific publications;
- Lack of clarity of symptomatic and/or disease-modifying treatment;
- Pathway circumvention over time;
- Litigation risks;
- Possible divergence in treatment response between the mild and moderate AD populations;
- The risk of inhibiting TNF entirely;
- Trial design risks.

9.4.1. Lack of substantial scientific publications

There is little scientific evidence on the action of filamin A in Alzheimer's disease, and there is little scientific evidence on the mechanism of action, which certainly originates outside of Cassava Sciences.

Although stated as part of Cassava's 2021 goals, no peer-reviewed publication confirming the science behind simufilam has been published, and the company does not seem to be pursuing such publication.

9.4.2. Lack of clarity of symptomatic and/or disease-modifying treatment

Simufilam's effect in Alzheimer's disease would lie in the inhibition of two faulty signaling pathways in Alzheimer's disease:

- From the amyloid plaques outside the cell, to the a7 nicotinic acetylcholine receptor on the cell surface, to hyperphosphorylate tau inside the cell; and

- From the amyloid plaques outside the cell, to the CD14 receptor on the cell surface, to the TLR4 receptor, to the creation of hyperphosphorylated tau inside the cell.

Simufilam's science is also based on targeting a misfolded scaffolding protein altered in Alzheimer's disease.

It is not certain at this stage which of these pathways is most influential to the treatment of Alzheimer's patients. It is not certain whether both of these pathways lead to disease modification. It is possible that simufilam combines a disease-modifying and symptomatic treatment, although the symptomatic treatment could be temporary.

It is possible that the first pathway leads to desensitization of the a7 nicotinic acetylcholine receptor. The most recent article from the Cassava Sciences team published on June 8, 2023 and entitled "Targeting α7 nicotinic acetylcholine receptors and their protein interactions in Alzheimer's disease drug development" mentions several previous efforts to target the same receptor and the risk of desensitization of such receptor. It also mentions the abandonment of several studies in different indications. The reasons for such abandonments have often not been stated.

9.4.3. Pathway circumvention or receptor overstimulation over time

An effect seen with many drugs is that over time, efficacy wears off due. This may be due to overstimulation of receptors or circumvention of pathways. Therefore, long-term efficacy data is important. With the exact pathways used by simufilam not fully detailed, the risk is real that the efficacy of simufilam could diminish over time. The 12-month data from Cassava Sciences' open-label study may give the first indication. The CMS study that is to be reported by Cassava Sciences in Q3 2023 and the Phase 3 trials data to be reported later may be of interest in that respect.

9.4.4. Litigation risks

Cassava Sciences has been the subject of criminal investigations and has been the target of short-sellers who also filed a well-researched Citizen's Petition and several additional letters and annexes. The Citizen's Petition was eventually denied, but it provided substantial information which may cast doubt over the scientific research and results communicated by Cassava Sciences. That doubt has hit mainstream media, as evidenced by articles in The Wall Street Journal and from other outlets. Cassava Sciences has filed proceedings against some of these short-sellers, which are ongoing.

One of the main reproaches is that the Cassava Sciences team may have tampered with their results, including the imaging results. In this regard, "exposing" possibly tampered-with photos on the basis of using cropped images instead of the raw data seems to be a business of its own, as there seems to be a constant flow of allegations by imaging experts that images may have been tampered with. An investigation into the publications of Dr. Wang at City University of New York is also ongoing. Several papers authored by Dr. Wang, including at least one related to the science behind simufilam, have been retracted by more than one scientific journal. In other cases, no evidence of manipulation has been found.

One of the other criticisms is that Cassava Sciences may have incorrectly communicated about biomarker measurements, having stated that the biomarkers in the open-label study were only taken at six months, meaning no biomarker results at 12 months from the open-label study were ever communicated. The relevant protocol states that for the first 50 patients, CSF biomarkers would be taken at six or 12 months (but not both). Cassava management reportedly stated in a fireside chat on April 5, 2022 that the company planned to measure biomarker changes in 25 patients before and after 12 months of open-label treatment.

It is hard to assess at this stage whether the Citizen's Petition had any scientific merit, apart from its obvious goal to result in financial gains from successfully shorting Cassava Sciences' stock.

9.4.5. Divergence in treatment response between the mild and moderate AD populations

On six occasions over the course of two years, Cassava Sciences has communicated cognitive data from an open-label study in approximately 200 patients with mild-to-moderate Alzheimer's disease over the course of one year.

- On the first occasion in February 2021, data for 50 patients over the course of six months showed a mean improvement of 1.6 points on the ADAS-Cog11 rating scale. No p-value was communicated.
- On the second occasion in July 2021, data for 50 patients over the course of nine months of treatment showed a mean improvement of 3 points on the ADAS-Cog11 rating scale. A p-value of <0.001 was communicated.
- On the third occasion in September 2021, data for 50 patients over the course of 12months of treatment showed a mean improvement of 3.2 points on the ADAS-Cog11 rating scale. A p-value of <0.001 was communicated.
- On the fourth occasion in August 2022, data for 100 patients over the course of 12months of treatment was communicated, showing a mean improvement of 1.5 points on the ADAS-Cog11 rating scale. A p-value of <0.05 was communicated.
- On the fifth occasion in January 2023, data for all patients over the course of 12 months of treatment was communicated, showing a mean slight decline of 0.5 points on the ADAS-Cog11 rating scale. No p-value was communicated, and a large difference between mild and moderate Alzheimer's patients was reported.
- On the sixth occasion in July 2023, placebo-controlled data from patients either on placebo or on simufilam after having been on simufilam for 12 months was communicated, showing a 38% slowing of cognitive decline. The result was not statistically significant, and a large difference between mild and moderate Alzheimer's patients was reported.

There has been skepticism about the reporting and selection process used by Cassava Sciences. There is a remarkable divergence between the mild sub-group, in which ADAS-Cog scores improved, and the moderate sub-group, in which ADAS-Cog scores worsened. The lack of p-value in the one-year open-label study results has led to the consideration that Cassava Sciences' results show placebo-like efficacy.

9.4.6. The risk of inhibiting TNF entirely

Traditional TNF inhibitors come with a serious risk of side effects in case of long-term use, such as improper defense against pathogens. Although the underlying science and proposed schematic MoA mention the reduction of cytokines such as TNF by simufilam, Cassava Sciences has not shared data on the reduction of TNF, insofar as we know. Inhibition of inflammation should not unselectively lead to the entire reduction of any inflammation unrelated to the disease itself, such as amyloid plaques and neurofibrillary tangles, as this may prevent the homeostatic and normal phagocytic and nurturing functions of glial cells. The proposed MoA of simufilam does not indicate that such would be the case, as the reduction of inflammation should be specific to hallmarks of Alzheimer's disease. There is also a publication on XPro which mentioned that soluble TNF is a key proinflammatory product of TLR4

signaling, which could indicate that the TLR4 pathway primarily results in production of soluble TNF. Of note, this publication was in research on opioid tolerance; Cassava Sciences was previously called Pain Therapeutics, and its scientific expertise in that field should be large.

For full information, taking into account the long duration before symptom-onset, the multitude of metadata-based publications showing the benefit of traditional non-brain-penetrant TNF-inhibitors in the prevention of Alzheimer's may indicate that broad TNF inhibition may be efficacious as well.

9.4.7. Trial design risks

Cassava Sciences has two 12-month Phase 3 trials ongoing in mild-to-moderate Alzheimer's disease, slated for results presumably some time in late 2024 or 2025.

The above results have shown that there appears to be a wide divergence between treatment populations, the reason for which at this point is unknown. Insofar as we know, Cassava Sciences has not shared elaborate thoughts on the possible reasons for that divergence on the basis of biomarkers in treated patients, or otherwise. Therefore, it is possible that the same or an even stronger divergence may be seen in placebo-controlled trials, which may place these trials at risk of achieving statistical significance.

As Alzheimer's is considered a multifactorial disease, it is possible that simufilam has little to no effect in certain subpopulations. Cassava Sciences has not proven that an altered conformation of filamin A is found in all patients with Alzheimer's disease.

Additionally, the traditional cognitive rating scales ADAS-Cog12, ADCS-ADL, iADRS, NPI, MMSE and CDR-SB, as used by Cassava Sciences as primary and secondary endpoints, could show a ceiling effect in some patients. Therefore, the trial results may not fully represent every cognitive change in every patient, which may lead to reduced changes in efficacy and statistical significance. The number of cognitive rating scales should reduce that risk, in light of possible consistency of results.

9.4.8. Unique focus on Alzheimer's disease

Cassava Sciences has one drug in its pipeline and is focused on one indication: Alzheimer's disease. While this may be helpful for an easy understanding of the company's stage of progress and from a valuation perspective, any negative or positive result will always relate to this drug for the said indication. That may result in high stock-price volatility.

9.5. Risks for Coya 301 and Coya Therapeutics

We highlight four possible risks with regards to Coya Therapeutics and its treatment candidates:

- Lack of substantial scientific publications;
- Possible divergence in treatment response between the mild and moderate AD populations;
- The risk of pathway circumvention;
- The risk of suppressing immune response entirely;
- Trial design risks;
- Coya may be considered an early-stage company.

9.5.1. Lack of substantial scientific publications

Insofar as we are aware, a rather limited dataset is available with regards to modulating Tregs with low-dose IL-2 for the treatment of neurodegenerative diseases, and AD more specifically. Some scientific publications, in part by the team around Coya, are mentioned on the company's website.

Therefore, the long-term consequences of low-dose IL-2, whether or not in combination with another treatment, are not fully known.

9.5.2. Divergence in treatment response between mild and moderate AD population

Coya's results so far do not indicate a divergence in treatment response between less- and further-progressed populations of patients. The open-label studies in both AD and ALS were small, however, meaning only limited information can be distilled from them in this respect.

As Alzheimer's is considered a multifactorial disease, it is possible that Coya 301 or other treatment candidates may have limited or no effect in certain subpopulations. Coya has not proven that Treg dysfunction is the cause of Alzheimer's in all patients with the disease.

9.5.3. Pathway circumvention or receptor overstimulation over time (low risk)

An effect seen with many drugs is that over time, efficacy wears off. This may be due to overstimulation of receptors or circumvention of pathways. Therefore, long-term efficacy data is important.

Due to the mechanism of action of Coya's drugs, primarily stimulating the activity of regulatory T cells and not just affecting one pathway, the risk is considered low in this case.

9.5.4. Trial design risks

Coya will pursue the treatment of ALS first in an upcoming Phase 2 trial. At this stage, the trial design does not feature subgroups, and hence, it incurs the risk that also non-responders could enter the trial. The same could happen in an upcoming trial for the treatment of AD.

9.5.5. Coya may be considered an early-stage company

Coya's IPO took place in December 2022, and since then, the company has announced wonderful data but has also replaced the treatment of frontotemporal dementia with the treatment of AD in its pipeline. Its pipeline features further treatment candidates. It is typical for early-stage biotech companies to reassess the potential of their pipeline at various stages. The need to pick up money with the accompanying dilution of shareholders, either with successful or unsuccessful reporting, is also typical for early-stage biotech companies.

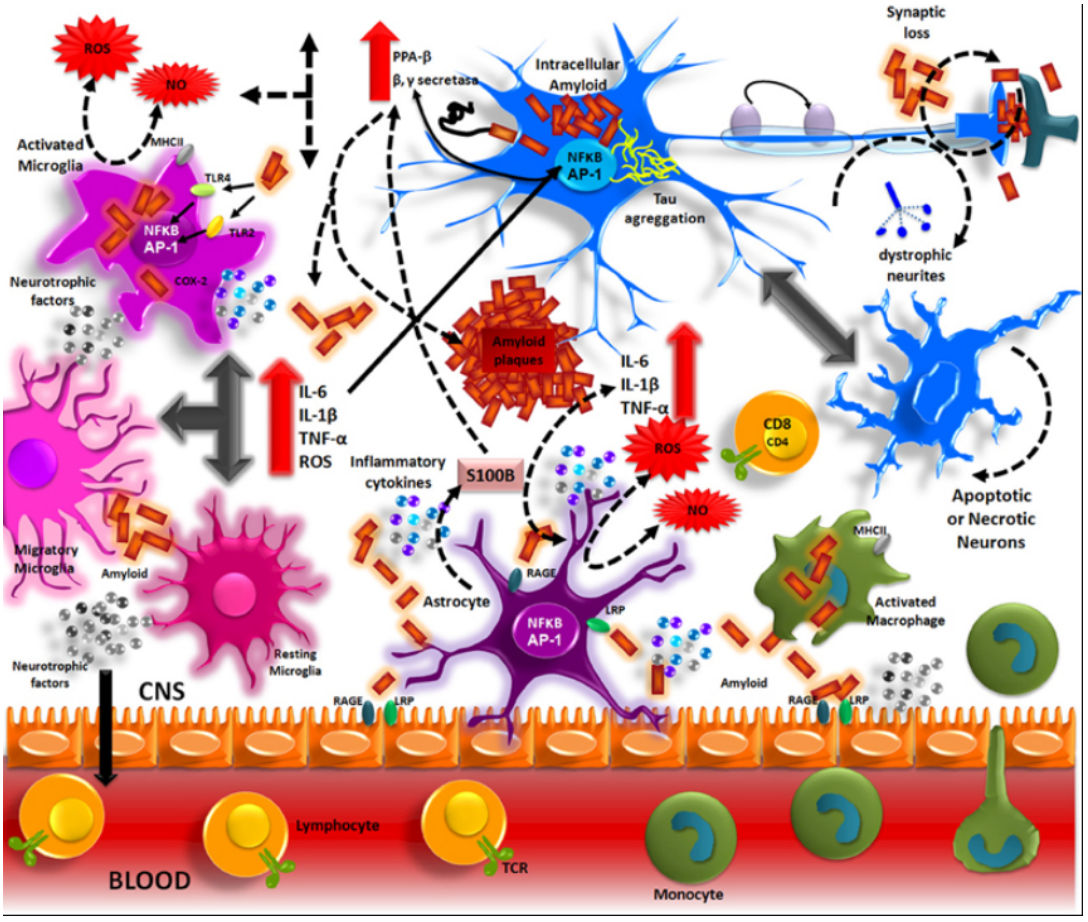
Nonetheless, Coya's pipeline may look very different in the not-so-distant future. Coya will launch a Phase 2 trial in ALS with Coya 302 in 2023 and will report on a placebo-controlled Phase 2 trial in Alzheimer's disease with Coya 301 in the second quarter of 2024,which may, in turn, trigger a further pipeline evolution, either into a Phase 3 trial with Coya 301 or a Phase 2 trial with a combination therapy including Coya 301.

10. A focus on reported biomarkers

10.1. Introduction

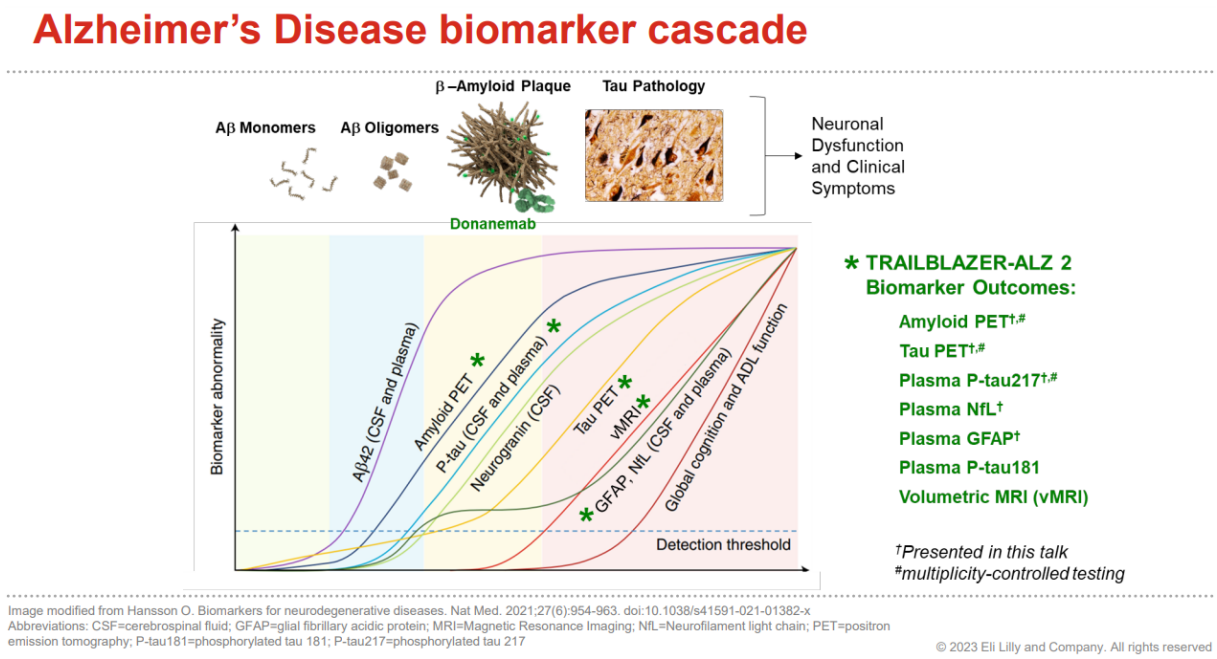
The further any disease progresses, the less chances there are of timely intervention, and the greater chances there are of reaching a floor effect, as seen in the rating scales currently used for Alzheimer's disease. Therefore, early detection is important.

Biomarkers may be able to allow for more precise readings of clinical development and enable a diagnosis earlier in the disease process to allow for more timely intervention. A correct analysis of biomarkers may allow more insight into a drug's efficacy. An understanding of the disease's biology and combined reading of several biomarkers may be relevant to this analysis. About 75% of AD-risk genes are microglia-specific, and inflammatory biomarkers were found to be predictive of Aβ deposition. The APOE4 gene may be highly relevant here, as it appears to exacerbate inflammation through NF-kB activation. Both APOE4 homozygotes and heterozygotes progress faster and bring a greater risk of dementia. The risk of Alzheimer's disease is three to four times higher in APOE4 heterozygotes and 12 to 14 times higher in homozygotes. TREM2 is also a genetic risk factor for Alzheimer's disease through impaired containment of inflammatory processes.



Source: V. Campos-Peña et al., Inflammatory Process in Alzheimer's Disease, Frontiers in Integrative Neuroscience 7(59):59, August 2013.

Biomarkers are also dependent on the stage of disease, with amyloid appearing first and biomarkers of glial activity and neurodegeneration rising much later in the progression of the disease.



Source: Eli Lilly AAIC 2023 presentation on donanemab / Eli Lilly corporate website.

Next to more traditional biomarkers such as Aβ40, Aβ42 and tau levels, markers of inflammatory activity through ROS, NF-kB, RAGE and TLR4 receptors/pathways, with effects on levels of IL-1, IL-6 and TNF, or markers of activation of microglia or astrocytes such as sTREM2, could be relevant here.

10.2. Biomarker reporting from anti-amyloid antibodies and other approaches

Assessment of drug potential taking biomarkers into account may be as equally important as looking at cognition results. The field of AD is rapidly progressing, and some biomarkers are more customarily included in trials and reported.

We have included reported biomarkers for three anti-amyloid antibodies, Eli Lilly's donanemab, Eisai/Biogen's lecanemab and Roche's gantenerumab, and the three drug candidates for INmune Bio, Cassava Sciences and BioVie, respectively. Lacking enough data for Coya 301 in AD at this point, biomarker data for this treatment candidate has not been included. Please note that gantenerumab recently failed a Phase 3 trial. This chart does not aim to be exhaustive and is subject to permanent updates.

	DONANEMAB	LECANEMAB	GANTENERUMAB		XPRO	SIMUFILAM	NE3107	COYA 301
MOA	Anti-amyloid, mostly plaques, specifically pyroglu-Aβ within plaques,	Anti-amyloid, protofibrils mostly	Anti-amyloid, fibrils mostly		Soluble TNF Inflammation	Filamin A Inflammation	Targeting inflammation through modulation of ERK and NF-kB	Targeting inflammation by rebalancing Treg activity
TARGET GROUP	MCI / Mild AD	MCI / Mild AD	MCI / Mild AD		MCI / Mild AD	Mild to moderate AD	Mild to moderate	/

COGNITION	Phase 3: - iADRS: 35% slowing of cognitive decline - CDR-SB: 36% slowing of cognitive decline - ADCS-iADL: 40 % slowing - Adas-Cog13: 30% slowing	CDR-SB 27% slowing of cognitive decline Adas-Cog 14 (47% slowing – Phase 2) ADCOMS (30% slowing – Phase 2) ADCS-MCI ADL	/ Trial failure		/ (indications of cognitive improvement in Phase 1 study – to be confirmed in placebo-controlled Phase 2 trial)	Open label study in 200 patients over 12 months: - ADAS-Cog11 : + 0.5 points (lower is better) - MMSE scores: - 1.3 points (lower is worse) - NPI10: - 0.3 points - GDS: 0.4 points	Open label study in 23 patients over 3 months: - Adas-Cog12: -0.91 points (lower is better) - MMSE: -0.75 points (lower is worse) - MoCa: -0.04 points - QDRS: -0.54 points (lower is better) - ADCOMS: 0.0049	Stat. significant improvement in mean MMSE scores. No cognitive decline on ADAS-Cog and CDR-SB scales.
NFL	No clear pattern.	No change in CSF. Trend towards improvement in plasma.	Slowing of rise / Less increase than placebo		-8% (3 m.)	-55% (6 m. / first 50 patients doing remarkably better than second 50 patients)	/	/
AB	71% achieved clearance (12m)	Mean change in centiloids at 18 months: -55.5. Mean amyloid PET 22.99 centiloids. Threshold for amyloid positivity is 30 centiloids.	Reduction on average of 59 centiloid on florbetapir PET at 48 weeks. 80% below threshold at 3 years.		/	/	/	/
P-TAU217	-35% at 76 weeks	/	/		- 46% (3 m.)	/	/	/
P-TAU181	Reduction.	-16% (18m.)	Reduction by about a third		Less than p-tau 271	-18% (6 m.)	/	/
TOTAL TAU	Reduction in trailblazer – ALZ1 study.	-4% (18m.)	Reduction by about a third		/	-38% (6 m.)	-3% (3 m.)	/
AB42/40 RATIO (LOWER IN AD / REFLECTS ACTIVE DEPOSITION)	+4% vs +2% placebo	+10% plasma, +60% CSF (18m.)	Up significantly / Returned to normal while worsening in placebo		/	/	-5.67% (3 m).	/
AB42	/ (to be reported)	Normalization.	Normalization		/	+84% (6 m.)	+4.1% (3 m.)	/
AB40	/ (to be reported)	Not affected.	/		/	/	/	/
PTAU / AB42	/ (to be reported)	/	/		/	/	-5.67% (3 m.)	/
INFLAMMATORY MARKERS	/	/	/		O-Link inflammatory markers: -15% (3 m.)	/	TNF – no exact numbers Reduction in TNF	Stat. significant reductions in CCL11, CCL2, IL-15,

					Free water: -5% (3 m.), -45% (12 m.)		correlates with positive cognitive results	TNFα, IL-6, IL-1β.
YKL-40	/	/	/		+285%	-44% (6 m.)	/	/
HMGB1	/	/	/		/	-53% (6 m.)	/	/
STREM2	/	/	/		/	-65% (6 m.)	/	/
(MICRO)GLIOSIS	Increase	/	/		/	/	/	/
GFAP	-19% at 76 weeks	-15% (18m.)	/		/	/	/	/
ALBUMIN	/	/	/		/	-15% / - 29% low and high dose	/	/
NEUROGRANIN	/	-15% (18m.)	/		-56% (3 m.)	-72% (6 m.)	/	/
CONTACTIN-2	/	/	/		+222%	/	/	/
VILIP-1	/	/	/		-91% (3 m.)	/	/	/
TREGS	/	/	/		/	/	/	Enhancement of Treg suppressive function and numbers (link to PR).
OTHER BIOMARKERS OF INTEREST	/	Decline in whole brain volume. Decline in cortical thickness. Decline in lateral ventricular volume. (Minor) improvements in total, left and right hippocampal volume.	/		**Radial diffusivity** : --16% (12 m). **Apparent fiber density** : +5% (3 m.), +17% (12 m.)	/	**DNA methylation** : -3.3 years reduction Horvath SkinBlood clock Modest improvements seen with arterial spin (**ALS**) and blood-oxygen dependent (**BOLD**) imaging.	/
TREND	Positive. pTau and GFAP keep dropping after sufficient amyloid removal.	Positive on amyloid removal and cognition in comparison to placebo. The slope of decline, particularly when looking at Adas-Cog14, may indicate faster decline than placebo after 15 months (slide 67).	/		Positive (biomarkers show strong upward trend)	Mixed (mild AD: positive, moderate AD: negative)	/	/
SAFETY	ARIA-E 27%	ARIA-E 12.5% ARIA-H 17%	ARIA-E 30%		No safety issues reported so far	No safety issues reported so far	No safety issues reported so far	Well tolerated. Mild

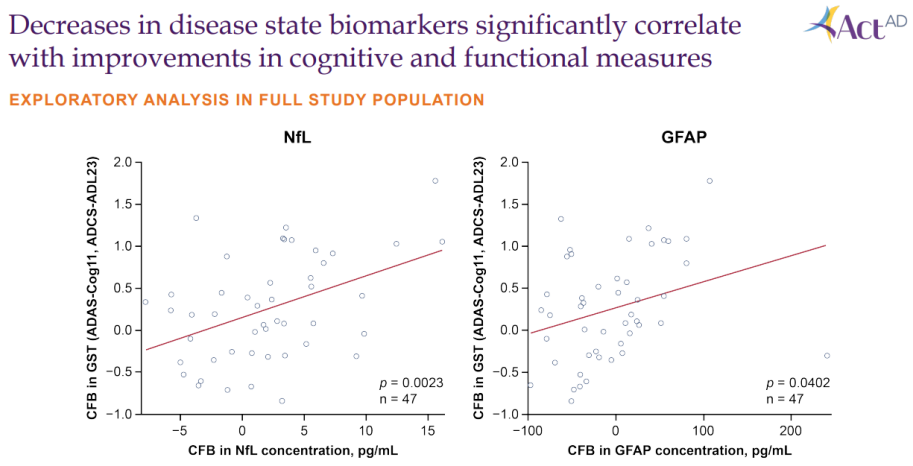
								injection site reactions.
ADMINISTRATION	Monthly infusions until amyloid drops below 25 centiloids.	Subcutaneous infusion Future: brain shuttle	Subcutaneous infusion		Subcutaneous shot (like insulin shot)	Oral	Oral	Subcutaneous.
LOSS OF BRAIN VOLUME	Yes.	Yes.	/		/	/	/	/

We highlight one additional biomarker of synaptic dysfunction that we consider relevant.

Neurogranin (synaptic dysfunction)

Company	Value reported
Cassava Sciences	-32% - 28 days -72% - 6 months
INmune Bio	-56% - 3 months
Anavex	Under investigation – Phase 2/3 trial
Annovis	Not reported / not found
Biogen – aduhelm	Not reported / not found
Biogen – lecanemab	-15% (18 months)

The author also actively looks for measures of GFAP, or glial fibrillary acidic protein, a marker of glial activation. In Eli Lilly's randomized Phase 1b and Phase 2 studies of donanemab, GFAP changes appeared to predict cognitive changes over time. In July 2023, Athira Pharma reported that change from baseline in GFAP concentration significantly correlated with improvements in ADAS-Cog11, and change from the double-blind period baseline in GFAP concentrations trended toward correlation with improvements in MMSE scores. GFAP improvements significantly correlated with a composite score of cognition and function.



Source: Athira Pharma corporate presentation.

As to measuring levels of phosphorylated tau, ptau217 seems the more exact biomarker. In Eli Lilly's Phase 1b and 2 trials of donanemab, ptau217 changes appeared to predict cognitive changes over time.

The author considers that sTREM2, a biomarker of microglial activation reported by some companies, may be a less-clear biomarker to identify the effect of treatments. Levels of sTREM2 appear to change throughout the course of disease and peak at the MCI stage, and contradictory reporting has been made with regards to correlation with the disease and other biomarkers.

10.3. A word on neurofilament light chain

10.3.1. Introduction

Neurofilament light chain recently made its regulatory debut, and the FDA seems to accept it as an endpoint in ALS and actively inquires about it in the framework of that disease. As it is a marker of neurodegeneration that may be useful in different neurodegenerative diseases, it merits some additional attention.

Neurofilaments, the larger group to which NfL belongs, are structural components of the neuronal cytoskeleton that are abundant in large myelinated axons. They have several biological functions, including stability and growth of axons, conduction properties, stability of mitochondria, and maintaining the structure and function of dendritic spines. They also play a role in regulating glutamatergic and dopaminergic neurotransmission at the synaptic level. As a consequence of axonal damage or degeneration, neurofilaments are released into the cerebrospinal fluid (CSF) through the axonal plasma membrane. They leak into the extracellular fluid and hence, into the CSF, penetrating the blood and thus behaving generally as a relatively non-specific marker of neuroaxonal pathology.

Neurofilament light chain (NfL), a biomarker for different neurodegenerative diseases, is a neuronal protein highly expressed in large-caliber myelinated axons. Its levels increase in CSF and blood proportionally to the degree of axonal damage in a variety of neurological disorders, including inflammatory, neurodegenerative, traumatic and cerebrovascular diseases. It is encoded by the NEFL gene, can be measured with immunoassays in cerebrospinal fluid and plasma, and is used as a biomarker reflecting axonal damage in a wide variety of neurological disorders. NfL in the serum increases with age, and NfL levels in the CSF and blood are altered in patients with CNS diseases. As they correlate with disease characteristics and are a quantitative measure of ongoing axonal injury, they can be used to monitor disease progression and, ideally, to evaluate patients' responses to treatments.

10.3.2. Neurofilament light chain as a diagnostic and treatment-predictive biomarker in neurological disorders

NfL is increased in the cerebral spinal fluid in a wide range of neurological disorders, with the highest amounts seen in ALS patients. Although they are unspecific to the type of neurologic disease, they are good identifiers of disease progression and drug effect. Purely in neurodegenerative diseases, NfL could serve as both a disease-prognostic and efficacy biomarker of experimental therapies. The more levels of NfL go down with treatment, the more it becomes likely that the disease is being treated and the patient is improving, without saying anything about what the underlying mechanism of action is.

There is a clear link with increased NfL in neurodegenerative diseases, demyelinating conditions and inflammatory CNS. In dementia trials, it is being used in almost every trial that's currently set up.

10.3.3. Neurofilament light chain in AD

CSF-NfL holds the potential to be a measure of both amyloid-dependent and independent neuronal loss, which is relevant if considering the contribution of different proteinopathies, vascular disease and neuroinflammation in AD pathophysiology.
In AD, the levels of NfL in CSF are increased years before symptoms of the disease appear. NfL changes in blood appear to precede the first clinical manifestations of AD by about 16 years, and a peak in the rate of increase in blood NfL has been observed around the onset of symptoms, thus suggesting that NfL marks the onset and intensity of neurodegeneration in AD.
There appears to be a correlation between NfL and cognition. In a meta-analysis covering 37 trials, higher levels of NfL have been reported to be associated with decreased cognitive performance, although the relationship was considered not to be universal, possibly due to the type of neurological disorder, differences between patients, or methodological inconsistencies. NfL was related to the domains of attention, memory, visuospatial effects, language, information processing and executive functions. Still, in AD, increased levels of NfL were seen as indicative of white-matter lesions, and hence, NfL could serve as a biomarker of white-matter integrity.
Elevated plasma neurofilament light has been reported to predict a faster rate of cognitive decline over five years in participants with objectively-defined subtle cognitive decline and mild cognitive impairment (MCI). It was shown that CSF-NfL levels were higher in an AD dementia group and in a stable MCI group and in a progressive MCI group compared to a healthy control group. In MCI, cognitively healthy individuals with higher CSF-NfL values have a threefold higher risk of MCI over a median follow-up of 3.8 years. CSF t-tau, phosphorylated tau (p-tau) and neurogranin were not found to have similar potential as predictors of MCI.
Baseline plasma NfL was also considered more strongly associated with cognitive and neuroimaging outcomes compared to T-tau, although ptau-217 has been reported to be a good predictor of cognitive decline.
At the AAIC Alzheimer's conference in July 2023, Athira Pharma presented biomarker data from its Phase 2 clinical trial showing that changes from baseline in NfL concentrations were significantly correlated with improvements in ADAS-Cog11, and changes from the double-blind period baseline in NfL concentrations were significantly correlated with improvements in MMSE scores at the transition to the open-label extension study. NfL was reported to be significantly correlated with a composite score of cognition and function.

10.3.4. NfL in other neurodegenerative diseases

NfL appears relevant, to some degree, in different neurodegenerative diseases. Higher levels of NfL have been associated with decreased cognition, specifically, poorer performance on measures of working memory, information-processing speed for executive functions, verbal fluency, attentional control, and verbal, episodic, and semantic memory[28].

As stated earlier, in ALS, the elevated NfL levels in cerebrospinal fluid (CSF) exceed those observed in most other neurological diseases where it also correlates with disease progression and can provide prognostic information. Due to the rapid degeneration of motor neurons (cells with large myelinated

[28] It was also considered useful in other degenerative diseases such as Hunter's syndrome, CLN2, multiple sclerosis, or spinal muscular atrophy. On June 20, 2023, in Hunter's syndrome, Denali Therapeutics reported an average reduction of 64% (p <0.001) from baseline in serum NfL after 2 years of dosing with DNL310.

axons containing a great amount of neurofilaments), CSF-NfL levels are increased more than sevenfold in ALS patients compared to neurologically healthy controls. NfL is also associated with survival, according to nearly all studies conducted on CSF, serum and plasma.

In multiple sclerosis (MS), blood NfL concentrations could identify acute and chronic neuronal damage, so increasing NfL could predict disease worsening and brain and spinal cord atrophy. Additionally, a decrease in NfL is correlated with a positive response to treatment. Serum NfL can predict long-term clinical outcomes in this disease, with a serum-NfL cutoff of 7.62 pg/mL having been identified as a possible discriminator of future disease progression. Reductions of NfL have been reported for most treatments for relapsing MS, in line with the perceived hierarchy of treatment efficacies and with the greatest reductions seen following the most intensive treatments. The largest reductions in plasma levels were seen following alemtuzumab (48%), and the smallest reduction was seen with teriflunomide (7%), with the other agents falling in the middle. One study reported a significant reduction of 51% in CSF-NfL levels after 12 to 24 months of treatment with mitoxantrone in 35 patients with MS.

In Parkinson's disease, the relationship with cognition may be less clear, but increased levels of NfL did predict a reduction in motor progression. Additionally, NfL has been reported to be increased in the parahippocampal cortex and is associated with the pathological hallmarks of Parkinson's disease dementia.

Increased NfL levels are also reported in frontotemporal dementia (FTD). On July 28, 2020, Alector reported a 29% reduction of NfL in its AL001 Phase 1b and Phase 2 open-label study over 28 weeks (seven months). On July 29, 2021, at 12 months in its Phase 2 study, it reported a 47% clinical slowing of progression and a change from 7.3 to 6.5 in NfL in CSF.

10.3.5. Recent accelerated approval based on NfL reductions in SOD1-ALS

Accelerated approval can occur on the basis of a biomarker which is predictive of efficacy. The first drug to receive accelerated approval in a neurological indication was Biogen's Aduhelm in 2021, on the basis of a reduction in amyloid-beta as a surrogate endpoint and without a direct link to cognitive benefit. NfL has become the second surrogate endpoint in ALS, again without a clear link to cognitive benefit. NfL has the potential to surpass amyloid-beta as surrogate endpoint across neurodegenerative diseases, not only in the framework of accelerated approval but also for full approval.

In the framework of the approval process for Amylyx's, Albriova, the former president of the FDA's department of neurology mentioned the importance of NfL:

"It's something we found to be part of the overall character of data that we see that does not support robust data for the primary measurements," Billy Dunn said. "In the interest of having an effective medication available for ALS patients, all of us would have preferred to have seen a benefit … that we didn't is a concern."

Treatment with Biogen's tofersen showed favorable results on neurofilament light, despite missing its primary endpoint in a Phase 3 trial. Although Biogen's Phase 3 trial did not show statistical significance on the primary and secondary endpoint, it did reveal a 55% reduction in NfL over 28 weeks. Meanwhile, patients who had been on the placebo saw a 44% decline in NfL levels when they were put on the drug in the open-label extension study. Biogen had determined that every 10 picogram per milliliter drop in NfL blood levels up to day 113 (nearly four months after treatment

initiation) predicted a 0.77-point slower reduction in ALSFRS-R scores up to day 197 (about 6.5 months).

Biogen filed for accelerated approval for the drug tofersen in ALS with an SOD1 mutation on August 5, 2022. Prior to the meeting of the FDA's advisory committee (AdCom) on March 22, 2023, Biogen had submitted an extensive note on NfL (pages 33 to 47). At the meeting about tofersen on March 22, 2023, the AdCom unanimously voted 9-0 that the drug's effect on NfL levels led to a reasonable likelihood of a clinical benefit. The accelerated approval for tofersen was also based on its reduction of NfL levels.

10.3.6. Reporting of neurofilament light in the treatment of different neurodegenerative diseases

Other companies are also reporting meaningful reductions in NfL values with their treatments. The duration within which a reduction of NfL occurs is probably relevant here, so meaningful reductions may need to be looked at over a longer period of time.

Company (drug)	Indication	Reported Reduction in Neurofilament-Light Chain
INmune Bio (XPro)	**AD**	-84% in 3 months (12 weeks);
Cassava Sciences (simufilam)	AD	- 34% (100 mg) in 1 month / - 28% in 1 month (28 days - 50 mg) - 55% in 6 months
Annovis Bio (buntanetap)	AD	-6% in a month
Athira Pharma (fosgonimeton)	AD	-7.8% over 6 months
Roche (gantenerumab - failed trial)	AD	Slowed increases of 1,7% compared to 3,9% in placebo over 4 years.
Eisai (lecanemab)	AD	Trend towards improvement in plasma.
Alector (latozinemab for FTD)	**FTD**	-29% in 7 months
Eisai (tofersen)	**SOD1-ALS**	'-55% over 28 weeks
BrainStorm Cell Therapeutics	**ALS**	-15% from baseline / ~-20% compared to placebo*
Annovis Bio (bantenerutap)	**PD**	-10% in a month
Roche (Ocrevus)	**MS**	-43% for RRMS, -16% for PPMS, over 21 months
Novartis (ofatumumab)	MS	-8.7% at 3 months, -26.5% at 12 months, -23.8% at 24 months
Bristol Myers Squibb (ozanimod)	MS	-26.9% at 12 months, -19.7% at 24 months

Sell-side analysts now seem to be picking up on the relevance of these reports in light of the recent developments on the side of the FDA and its AdCom.[29]

[29] - H.C. Wainwright, Andrew Fein, research report on Biogen, October 5, 2021 entitled 'What Can We Learn From NfL as a Biomarker in Neuro Trials? —Implications for Biogen's Upcoming Phase 3 ALS Trial Data';

11. Conclusion

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.

Traditional treatment consists of administration of acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine. Donepezil was first approved in 1996, more than 20 years ago. These are symptomatic treatments that do not affect disease progression.

What followed were decades of trial failures. However, recent Phase 3 successes have been reported with anti-amyloid antibodies. The efficacy rates reported so far are modest; Leqembi and donanemab seem to allow for maximally a 25% to 40% slowing of cognitive decline in milder stages of disease, with quite a few side effects.

There are large unmet medical needs for the treatment of Alzheimer's disease. The efficacy of treatments should improve, and combination therapies should be considered, whether or not they're focused on the biology of aging. Additionally, side effects can be reduced, and further-advanced patient groups should be able to receive treatment as well.

Over the past two years, four publicly listed companies have reported data that seem to indicate that the progression of Alzheimer's disease can be stopped or reversed. This research report focused on their respective treatment candidates: BioVie's NE3107, INmune Bio's XPro, Cassava Sciences' simufilam and Coya Therapeutics's Coya 301.

These companies share similar outspoken ambitions to stabilize or improve cognition in Alzheimer's disease, and more than a few similarities between their mechanisms of action (MoA), onset and safety profile appear to exist. An analysis of the MoA rationale for the drug candidates from these different companies and an understanding of the value of biomarkers in AD may provide insights and validation of the new approaches, which we consider to have anti-inflammation and metabolic dysregulation as their common denominators.

The author believes that successful treatments of neuroinflammation and metabolic dysregulation, which are more novel hallmarks of neurodegenerative diseases, are commonalities seen in the aforementioned companies. There are many 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 proinflammatory 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.

The respective drug candidates of the aforementioned companies may bear more similarities than seen at first glance. They may all exert anti-inflammatory activity through TLR4, inhibition of ERK and JNK, inhibition of NF-kB, and improved insulin sensitization. Whereas simufilam may reduce inflammation through the a7nAChR receptor, among other avenues, NE3107 and XPro may both do

- Jefferies, Andrew Tsai, research report on Athira Pharma of May 11, 2023.

so by inhibiting pro-inflammatory TNFR1 signaling, leaving the beneficial signaling through TNFR2 unaffected. Coya pursues a similar goal with a different treatment in an effort to rebalance the immune system by modulating regulatory T cells.

The drug candidates of the aforementioned companies have seemingly safe profiles without serious side effects and seem to have much faster onsets than anti-amyloid therapies.

Each of these companies comes with different risks on their paths to success. Those risks include those related to litigation, administrative burden and trial design, among others.

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

BioVie's Phase 3 trial has enrolled patients with mild-to-moderate Alzheimer's disease and at first glance has not based its trial design on patient biology. However, the 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 U.S.-related hold being lifted.

Cassava Sciences' Phase 3 trials are large and ongoing and 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. On the basis of the recent data reported from a placebo-controlled Cognition Maintenance Study, the author's calculation of the cognitive decline in patients with moderate Alzheimer's disease, suggests that those patients' cognitive decline occurred faster than patients on placebo declined. 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).

Positive reporting of placebo-controlled trials in Alzheimer's generally coincides with substantial market-value gains in the concerned (big pharma) companies and substantial market value gains for related companies.

An understanding of the different biomarkers reported by the aforementioned companies and a comparison with data reported from successful anti-amyloid antibody therapies may allow for knowledgeable decisions as to efficacy and the potential for disease-modifying activity in the concerned therapies. Insofar as reported, this research note has tried to provide a comprehensive overview of biomarkers reported so far.

The goal of this research was to provide insights on 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.

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