Peer-Reviewed Scientific Publication Proposes Unifying Single Toxin Theory of Brain Neurodegeneration that Identifies New Drug Targets and Treatments for Alzheimer's Disease and Other Neurodegenerative Disorders

Soluble Beta Amyloid Aggregates Called Oligomers or Protofibrils Initiate and Drive Pathogenesis of Alzheimer's Disease

All Other Biochemical Effects and Neurodegenerative Changes Observed in Alzheimer's Brain Are a Direct Response to or Downstream Effect of Initial toxic Insult by Amyloid Oligomers

Other Neurodegenerative Disorders Follow Similar Path in which Normal Brain Proteins Become Trapped in Aging Brain Due to Impaired Clearance and then Misfold and Aggregate into Neurotoxic Species that Exhibit Prion-Like Behavior

Inhibition of Amyloid Misfolding and Aggregation by ALZ-801/Valiltramiprosate Could Slow Disease Progression in Alzheimer's Patients

FRAMINGHAM, Mass., March 26, 2024 — Alzheon, Inc., a clinical-stage biopharmaceutical company developing a broad portfolio of product candidates and diagnostic assays for patients suffering from Alzheimer's disease (AD) and other neurodegenerative disorders, today announced the publication of a peer-reviewed research paper, "The Single Toxin Origin of Alzheimer's Disease and Other Neurodegenerative Disorders Enables Targeted Approach to Treatment and Prevention" in the Special Issue Dementia: From Molecular Pathophysiology to Novel Therapeutic Approaches of the *International Journal of Molecular Sciences*, available through open access at: https://doi.org/10.3390/ijms25052727.

"Novel biomarkers and disease-modifying treatments have advanced our understanding of Alzheimer's and provide support for our thesis that the aggregation of misfolded native proteins initiates and drives the pathogenic cascade that leads to Alzheimer's disease and other age-related neurodegenerative disorders. In addition, our single toxin theory of brain neurodegeneration identifies new targets and approaches for the development of disease-modifying treatments," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon.

"Therapies such as oral ALZ-801/valiltramiprosate that inhibit beta amyloid misfolding and aggregation in this initial step of the amyloid cascade offer a tremendous opportunity to advance the standard of care for Alzheimer's disease. The results from our pivotal APOLLOE4 Phase 3 trial later this year evaluating ALZ-801 will provide an important data point for this approach and set the stage for the potential NDA submission this year and commercial launch in 2025."

Authored by Alzheon scientists, the publication reviews the pathogenic cascade leading to AD and offers insights into pathogenesis, as well as therapeutic approaches that can lead to disease modification and clinically meaningful benefits for patients with Alzheimer's and other neurodegenerative disorders. The publication profiles four anti-amyloid treatments that have progressed to late-stage clinical trials in AD and highlights the discoveries led by Alzheon scientists that enabled these advances:

- Identification of soluble amyloid oligomers as the upstream triggers of brain neurodegeneration and as drivers of Alzheimer's pathogenesis.
- The biological definition of AD based on biomarkers, which enabled improved diagnostic accuracy using the A/T/N (amyloid/tau/neurodegeneration) criteria.
- The application of biomarkers, in particular p-tau, synaptic markers, and brain volumetrics for the evaluation of disease course and therapeutic efficacy in AD trials.
- An improved understanding of the role of APOE4 genotype in Alzheimer's pathogenesis and its effects on efficacy and safety of anti-amyloid treatments.

To date, only agents that either block formation of or preferentially clear soluble amyloid aggregates have shown clinical efficacy in Alzheimer's clinical trials, suggesting that amyloid oligomers are the primary causative agents in AD pathogenesis. Other neurodegenerative disorders follow the same pattern of protein dysregulation, impaired clearance, and increased aggregation, leading to neurotoxicity and loss of function. In these diseases, a normal essential protein starts accumulating in the brain, misfolding and aggregating into soluble oligomers. These oligomers behave like prions, propagating and seeding further aggregation across synaptic networks, form pathognomonic protein aggregates that are toxic to specific neuronal populations and cause the degeneration of neuronal networks. The destruction of brain structures by oligomer assemblies results in characteristic clinical syndromes described in Alzheimer's disease and Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, and many other neurological diseases.

These well-conserved pathways of brain neurodegeneration offer multiple opportunities for potential disease-modifying interventions to slow the progression or even prevent the onset of clinical symptoms if administered early in the course of the pathogenic process. Therapeutic strategies to treat and prevent neurodegenerative disorders include interventions to improve the clearance of toxins from the brain and the use of agents that inhibit the misfolding of proteins, aggregation into oligomers, the toxicity of pathogenic aggregates, and prion propagation.

"The degree of amyloid oligomer selectivity appears to be the key factor that, together with the pharmacokinetic properties, determines the magnitude of the benefit and risk profile for each anti-amyloid agent," said co-author Susan Abushakra, MD, Chief Medical Officer of Alzheon. "ALZ-801 provides advantages over injectable antibodies as an oral agent that efficiently crosses the blood brain barrier, selectively interacts with amyloid monomers to inhibit their misfolding, and blocks the formation of neurotoxic soluble amyloid oligomers in a concentration-dependent manner, without affecting insoluble amyloid plaques or fibrils. Along with its well-differentiated anti-oligomer characteristics, ALZ-801 is the most advanced of the next generation of highly selective anti-oligomer agents in development and provides an innovative precision medicine solution in an emerging Alzheimer's pipeline, with a path to potential approval in 2025."

About ALZ-801

ALZ-801/valiltramiprosate is a potential first-in-class, investigational oral disease-modifying therapy in Phase 3 development for the treatment of early Alzheimer's disease. In mechanism-of-action studies, ALZ-801 fully blocked the formation of neurotoxic soluble beta amyloid (Aβ) oligomers at the Phase 3 clinical dose. ALZ-801 has shown potential for robust clinical efficacy in the highest-risk AD population – patients with two copies of the apolipoprotein ε4 allele (APOE4/4 homozygotes), and favorable safety with no increased risk of brain vasogenic edema. This population is the focus of Alzheon's pivotal Phase 3 APOLLOE4 trial, which is now fully enrolled and will be completed in mid-2024.

ALZ-801 Phase 2 Biomarker Trial

Biomarker Effects of ALZ-801 in APOE4 Carriers With Early Alzheimer's Disease (NCT04693520): This ongoing trial was designed to evaluate the effects of 265 mg twice daily oral dose of ALZ-801 on biomarkers of AD pathology in subjects with Early AD, who have either the APOE4/4 or APOE3/4 genotype and constitute 65-70% of Alzheimer's patients. The trial also included evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of ALZ-801 over 104 weeks of treatment. An ongoing long-term extension of the trial evaluates ALZ-801 for an additional 52 weeks of treatment for a total of 156 weeks.

ALZ-801 APOLLOE4 Phase 3 Trial

An Efficacy and Safety Study of ALZ-801 in APOE4/4 Early Alzheimer's Disease Subjects (NCT04770220): This ongoing trial is designed to evaluate the efficacy, safety, biomarker and imaging effects of 265 mg twice daily oral dose of ALZ-801 in Early AD subjects with two copies of the apolipoprotein ε4 allele (APOE4/4 homozygotes), who constitute approximately 15% of Alzheimer's patients. This is a double-blind, randomized trial comparing oral ALZ-801 to placebo treatment over 78 weeks. The APOLLOE4 trial is supported by a $51 million grant from the National Institute on Aging.

About Alzheon

Alzheon, Inc. is a clinical-stage biopharmaceutical company developing a broad portfolio of product candidates and diagnostic assays for patients suffering from Alzheimer's disease and other neurodegenerative disorders. We are committed to developing innovative medicines by

directly addressing the underlying pathology of neurodegeneration. Our lead Alzheimer's clinical candidate, ALZ-801/valiltramiprosate, is a first-in-class oral agent in Phase 3 development as a potentially disease modifying treatment for AD. ALZ-801 is an oral small molecule that has been observed to fully block the formation of neurotoxic soluble amyloid oligomers in preclinical tests. Our clinical expertise and technology platform are focused on developing drug candidates and diagnostic assays using a precision medicine approach based on individual genetic and biomarker information to advance therapies with the greatest impact for patients.

Alzheon Scientific Publications

[1] Tolar M, et al: *The Single Toxin Origin of Alzheimer's Disease and Other Neurodegenerative Disorders Enables Targeted Approach to Treatment and Prevention,* **International Journal of Molecular Sciences,** 2024; 25, 2727.

[2] Tolar M, et al: *Neurotoxic Soluble Amyloid Oligomers Drive Alzheimer's Pathogenesis and Represent a Clinically Validated Target for Slowing Disease Progression*, **International Journal of Molecular Sciences**, 2021; 22, 6355.

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[4] Tolar M, et al: *Aducanumab, Gantenerumab, BAN2401, and ALZ-801—the First Wave of Amyloid-Targeting Drugs for Alzheimer's Disease with Potential for Near Term Approval, **Alzheimer's Research & Therapy**,* 2020; 12: 95.

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