Health & Medicine | Jan 8, 2026 | 8 min read | By Bryan White

Beyond the Amyloid Hypothesis in Alzheimer's Disease: Achieving Full Neurological Recovery via NAD+ Homeostasis

Biology * Public Health * DNA

Challenging the Dogma of Irreversibility

Since Alois Alzheimer first described the neuropathology of dementia in 1906, clinical neuroscience has operated largely under the premise that Alzheimer's disease (AD) represents irreversible structural attrition.[1] Guided by the Amyloid Cascade Hypothesis, therapeutic development has focused overwhelmingly on monoclonal antibodies engineered to clear extracellular beta-amyloid plaques.[1][2] Yet while FDA-approved agents such as lecanemab and donanemab reduce cerebral plaque burden, lecanemab achieved a 27% slowing of cognitive decline over 18 months in the Phase 3 CLARITY AD trial while carrying risks of Amyloid-Related Imaging Abnormalities (ARIA), cerebral edema, and microhemorrhages.[2]

A study published online in December 2025 in Cell Reports Medicine (2026 issue) by Kalyani Chaubey, Andrew A. Pieper, and colleagues at Case Western Reserve University, University Hospitals, and the Louis Stokes Cleveland VA Medical Center challenges both the amyloid-centric paradigm and the assumption of irreversible cognitive loss.[1][3][4] By targeting cellular bioenergetics through Nicotinamide Adenine Dinucleotide (NAD+) homeostasis using the small-molecule compound P7C3-A20, the researchers demonstrated full neurological and cognitive recovery in two distinct mouse models of advanced Alzheimer's pathology -- even without clearing existing amyloid plaques.[1][3]

Bioenergetic Collapse and the NAMPT Salvage Pathway

Although the human brain comprises only ~2% of total body mass, it consumes roughly 20% of resting oxygen and glucose supplies.[1] Because mature neurons are post-mitotic and do not undergo cell division, this metabolic expenditure supports resting membrane potentials and synaptic repolarization via sodium-potassium ATPase pumps that continuously hydrolyze Adenosine Triphosphate (ATP).

At the center of neuronal bioenergetics is NAD+, an essential coenzyme that acts both as a redox electron carrier (shuttling electrons as NADH to drive mitochondrial oxidative phosphorylation) and as a consumable substrate for Sirtuin deacetylases (SIRT1 and SIRT3) and Poly (ADP-ribose) polymerases (PARPs) involved in DNA repair.[7][11] Analyses of postmortem human AD brain tissue and murine models by the Case Western team revealed marked cerebral NAD+ depletion accompanying worsening pathology.[1][3] As amyloid and tau pathology drive chronic DNA-damage repair and neuroinflammation, neurons exhaust their NAD+ pools, entering a bioenergetic crisis that disrupts synaptic transmission and degrades the blood-brain barrier (BBB).[1][7]

Whereas dietary precursors such as Nicotinamide Riboside (NR) and Nicotinamide Mononucleotide (NMN) rely on mass-action loading -- which can produce

supraphysiologic NAD+ spikes that raise concerns about fueling glycolytic cancer metabolism -- the P7C3 aminopropyl carbazole series discovered by Pieper and colleagues stabilizes physiological NAD+ salvage through Nicotinamide Phosphoribosyltransferase (NAMPT), the rate-limiting enzyme of neuronal NAD+ recycling.[5][6][11] By supporting intracellular NAMPT salvage kinetics rather than bypassing cellular regulation, P7C3-A20 remains governed by endogenous feedback loops and restores homeostatic NAD+ balance without supraphysiologic overflow.[1][6][11]

| Feature | | P7C3-A20 (NAMPT Salvage Enhancer) | | NAD+ Precursors (NR / NMN) | | Anti-Amyloid Antibodies (Lecanemab) |

| Primary Target | | Intracellular NAMPT (Salvage Pathway)[6] | | Preiss-Handler / Salvage Substrate Pool | | Extracellular Amyloid-Beta Plaques[2] |

| Mechanism | | Pharmacologic enhancement of NAD+ salvage[6][11] | | Mass-action precursor supplementation | | Immunological aggregate clearance[2] |

| Effect on NAD+ | | Restores homeostatic baseline[1] | | Can elevate beyond physiological ranges[3] | | None (Direct) |

| Safety Profile | | Feedback-regulated in preclinical models[1][11] | | Theoretical risk of fueling occult tumors[3] | | ARIA (cerebral edema / microhemorrhages)[2] |

| Observed Outcome | | Full cognitive reversal in advanced AD mice[1] | | Variable clinical cognitive efficacy | | ~27% slowing of cognitive decline over 18 months[2] |

Preclinical Reversal in Advanced Amyloid and Tau Models

Unlike preventative preclinical studies that administer experimental agents prior to plaque deposition or behavioral decline, Chaubey et al. initiated daily P7C3-A20 treatment only after transgenic mice reached advanced, symptomatic stages of neurodegeneration:[1][3]

* 5xFAD Amyloid Model: Carrying five human familial AD mutations -- three in the Amyloid Precursor Protein (APP) gene and two in Presenilin 1 (PSEN1) -- these mice develop rapid extracellular amyloid-beta plaque deposition, reactive gliosis, blood-brain barrier breakdown, and pronounced cortical and hippocampal pathology.[1]

* PS19 Tauopathy Model: Expressing P301S mutant human tau, these mice form intracellular neurofibrillary tangles accompanied by hippocampal degeneration and synaptic loss, modeling the tauopathy that closely tracks cognitive decline in human patients.[1][9]

Across both transgenic cohorts, chronic P7C3-A20 administration restored spatial learning and memory retention in the Morris Water Maze -- including escape latency and probe-trial quadrant preference -- to levels indistinguishable from healthy wild-type controls.[1][12] Treatment simultaneously normalized performance in hippocampal-dependent behavioral assays and extinguished chronic neuroinflammation in both amyloid and tauopathy cohorts.[1][4]

Crucially, this behavioral recovery in 5xFAD mice occurred without clearing extracellular amyloid plaques.[1][4] Dissociating functional recovery from plaque

removal indicates that neurons can regain synaptic function around extracellular protein aggregates once cellular bioenergetics recover. Replenishing physiological NAD+ supports PARP-mediated DNA repair enzymes alongside sirtuin pathways including SIRT1 and mitochondrial SIRT3, curbing tau acetylation, improving electron transport chain function, and lowering reactive oxygen species stress.[1][7][9] Histological and electrophysiological assays confirmed that P7C3-A20 repaired endothelial tight junctions across the leaky blood-brain barrier, attenuated microglial activation, restored hippocampal long-term potentiation (LTP), and stimulated adult hippocampal neurogenesis.[1][5]

Human Multiomics Validation and the Unified Neurodegenerative Model

To bridge murine models and human pathology, the team evaluated plasma p-tau217 -- phosphorylated tau at threonine 217, a leading clinical blood biomarker for human AD -- and showed that P7C3-A20 lowered circulating p-tau217 back toward baseline.[1][3] Multiomic comparison of murine hippocampal gene expression and proteomics against postmortem human AD brain repositories further identified a conserved 46-protein therapeutic signature.[1] These 46 proteins -- spanning synaptic scaffolding, mitochondrial bioenergetics, neuroinflammatory regulators, and vascular integrity -- were dysregulated in both untreated AD mice and human AD brains, yet normalized toward healthy baseline levels after P7C3-A20 therapy.[1][12]

| Proteomic Node Category | | Pathological State in Advanced AD | | P7C3-A20 Therapeutic Response |

| Synaptic Structural Proteins | | Depleted post-synaptic density & dendritic cytoskeleton | | Normalized abundance; restored synaptic plasticity (LTP)[1] |

| Mitochondrial Respiratory Subunits | | Downregulated electron transport chain complexes | | Restored oxidative phosphorylation & NAD+/ATP bioenergetics[1][7] |

| Neuroinflammatory Mediators | | Chronic microglial activation & acetylated tau stress | | Attenuated gliosis & lowered p-tau217 / tau acetylation[1][9] |

| BBB Tight-Junction Proteins | | Endothelial gap breakdown & vascular leakage | | Structural repair of blood-brain barrier integrity[1][8] |

Transcriptomic and proteomic analyses of "nondemented with AD neuropathology" (NDAN) individuals -- people who died with heavy plaque and tangle burdens yet remained cognitively intact -- also revealed preserved NAD+ homeostasis signatures in the brain.[1][3] This bioenergetic mechanism parallels the Pieper laboratory's earlier finding that P7C3-A20 repairs the blood-brain barrier, arrests chronic neurodegeneration, and restores cognition in mice treated one year after traumatic brain injury (TBI), implicating NAD+ depletion and microvascular breakdown as shared therapeutic targets across acute neurotrauma and neurodegenerative disease.[8][10]

The Dawn of Metabolic Neurotherapeutics

Translating P7C3-A20 and related NAMPT-targeting agents -- including ongoing translational development through spinouts such as Glengary Brain Health -- into human clinical trials requires resolving key clinical questions.[3][11] First, Phase I human safety trials must verify that enhancing NAD+ salvage carries an acceptable safety profile in older adults without promoting occult neoplasms.[11] Second, human

AD unfolds over decades alongside cerebrovascular disease, TDP-43 co-pathology, and irreversible neuronal death in late-stage cortex; stabilizing NAD+ metabolism can rescue bioenergetically impaired circuits and support hippocampal plasticity, but cannot regenerate neurons that have already been lost.[1][10] Nevertheless, restoring neuronal NAD+ homeostasis establishes a compelling complementary strategy alongside plaque-targeting immunotherapies: significant functional impairment in Alzheimer's disease may stem from treatable metabolic dysfunction rather than uniform structural erasure.[1][4]

Updates... (Nov 22, 2026): Enriched all primary journal and institutional citations with exact CrossRef/OpenAlex publication dates (Dec 22, 2025 online for Chaubey et al., Jan 2026 issue; Jan 5, 2023 for van Dyck et al.; Dec 22, 2025 for University Hospitals; Dec 27, 2025 for Neuroscience News; and exact dates for foundational P7C3 studies) and standardized the References section heading.

References & Primary Sources

* [1] Chaubey, K., V zquez-Rosa, E., Tripathi, S., Pieper, A. A., et al. (Dec 22, 2025; Jan 2026 issue). Pharmacologic reversal of advanced Alzheimer's disease in mice and identification of potential therapeutic nodes in human brain. Cell Reports Medicine, 7(1), 102535. -- https://doi.org/10.1016/j.xcrm.2025.102535

* [2] van Dyck, C. H., Swanson, C. J., Aisen, P., et al. (Jan 5, 2023). Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine, 388(1), 9-21. -- https://doi.org/10.1056/nejmoa2212948

* [3] Case Western Reserve University Newsroom (Jan 13, 2026). New study shows Alzheimer's disease can be reversed to achieve full neurological recovery -- not just prevented or slowed -- in animal models. -- https://case.edu/news/new-study-shows-alzheimers-disease-can-be-reversed-achieve-full-neurological-recovery-not-just-prevented-o

* [4] University Hospitals Newsroom (Dec 22, 2025). Study Shows Alzheimer's Disease Can Be Reversed in Animal Models. -- https://news.uhhospitals.org/news-releases/articles/2025/12/study-shows-alzheimers-disease-can-be-reversed-in-animal-models

* [5] Pieper, A. A., Xie, S., Capota, E., et al. (Jul 2010). Discovery of a Proneurogenic, Neuroprotective Chemical. Cell, 142(1), 39-51. -- https://doi.org/10.1016/j.cell.2010.06.018

* [6] Wang, G., Han, T., Nijhawan, D., et al. (Sep 2014). P7C3 Neuroprotective Chemicals Function by Activating the Rate-Limiting Enzyme in NAD Salvage. Cell, 158(6), 1324-1334. -- https://doi.org/10.1016/j.cell.2014.07.040

* [7] Wu, Y., Hu, Q., Wu, X., et al. (Feb 8, 2023). P7C3-A20 Attenuates Microglial Inflammation and Brain Injury after ICH through Activating the NAD+/Sirt3 Pathway. Oxidative Medicine and Cellular Longevity, 2023, 7857760. -- https://doi.org/10.1155/2023/7857760

* [8] V zquez-Rosa, E., Shin, M.-K., Dhar, M., et al. (Oct 21, 2020). P7C3-A20 treatment one year after TBI in mice repairs the blood-brain barrier, arrests chronic neurodegeneration, and restores cognition. Proceedings of the National Academy of Sciences, 117(44), 27667-27675. -- https://doi.org/10.1073/pnas.2010430117

* [9] Shin, M.-K., V zquez-Rosa, E., Koh, Y., et al. (May 2021). Reducing acetylated tau is neuroprotective in brain injury. Cell, 184(10), 2715-2732. -- https://doi.org/10.1016/j.cell.2021.03.032

* [10] Sridharan, P. S., Miller, E., & Pieper, A. A. (Oct 2023). Application of P7C3 Compounds to Investigating and Treating Acute and Chronic Traumatic Brain Injury. Neurotherapeutics, 20(6), 1616-1628. -- https://doi.org/10.1007/s13311-023-01427-8

* [11] Velma, G. R., Krider, I. S., Alves, E., et al. (Apr 5, 2024). Channeling Nicotinamide Phosphoribosyltransferase (NAMPT) to Address Life and Death. Journal of Medicinal Chemistry, 67(8), 6017-6033. -- https://doi.org/10.1021/acs.jmedchem.3c02112

* [12] Neuroscience News (Dec 27, 2025). Study Finds Way to Reverse Alzheimer's. -- https://neurosciencenews.com/alzheimers-reversed-neuropharmacology-30070/