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NAD⁺, a Metabolic Currency, Repairs Alzheimer's Phenotypes in Mice

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According to a recent study, the view that Alzheimer's disease damages the brain irreversibly might need to change. In December 22 Cell Reports Medicine online, scientists led by Andrew Pieper of Case Western Reserve University, Cleveland, report that boosting levels of the metabolic coenzyme NAD⁺ in two different Alzheimer's disease mouse models prevents measures of disease in younger mice and normalizes them in older mice. Raising the mice's supply of NAD⁺ with the compound P7C3-A20 rescued a lengthy catalog of pathologies and toggled protein levels away from aberrant signatures in mice and humans with AD.

- Small molecule P7C3-A20 restores NAD⁺ supply in AD mouse models.
- P7C3-A20 reversed pathologic changes in plaque, phospho-tau, blood-brain barrier structure, synaptic function, and behavior assays.
- P7C3-A20 flipped proteome changes in 5xFAD mice; some mirror alterations in people with AD.
- Next step: clinical development.

"Our results are very encouraging," Pieper wrote to Alzforum. "Seeing P7C3-A20 reverse signs of disease in two different mouse models of AD, one driven by A β plaques and one by tauopathy, strengthens the idea that restoring the brain's NAD⁺ balance might help people recover from AD."

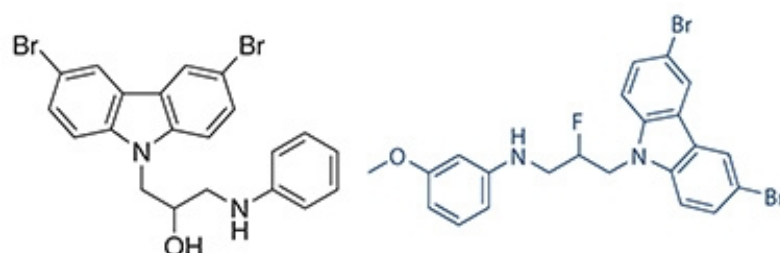
Russell Swerdlow, University of Kansas Medical Center, Kansas City, agrees with this idea. "This work supports the view that fixing dysfunctional bioenergetics or carbon fluxes within a brain can benefit that brain, potentially even those impacted by AD," he told Alzforum.

Previously, Pieper, working at the time with Steven McKnight at the University of Texas Southwestern Medical Center, Dallas, had pinpointed P7C3 as a compound promoting neurogenesis in a drug screen in mice ([Jul 2010 news](#)).

Next came the question of whether boosting the brain's NAD⁺ supply could have therapeutic promise in Alzheimer's, as some of the manifold processes this metabolite is involved in go awry in the disease. NAD⁺ is central to ATP production, plus it performs non-enzymatic roles in cell signaling, DNA repair, epigenetic remodeling, and axonal health ([Chini et al., 2024](#); [Wang et al., 2021](#)).

In this study, first author Kalyani Chaubey and colleagues tested a follow-up compound to the original P7C3, P7C3-A20, in 5xFAD mice. Pieper claimed this improved analog has “improved neuroprotective activity.” They do not yet know the exact mechanism by which this compound acts.

The scientists injected mice intraperitoneally every day from 2 to 6 months of age to assess potential preventive effects in what they called the model's “mid-disease” stage, and treated a separate group from 6 to 12 months to evaluate reversal of behavioral deficits and AD pathologies in more advanced disease. These mice survive for approximately 18 months (Nehra et al., 2024).



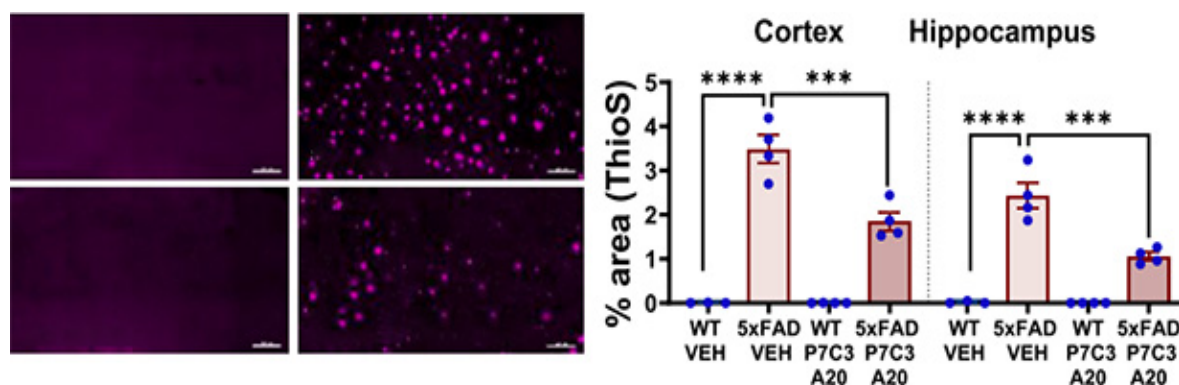
A Better Structure? Chemical structures of P7C3 (left) and the second-generation analog P7C3-A20 (right).

[Courtesy of Andrew Pieper.]

At 2 months, 5xFAD mice had NAD⁺ levels similar to wild-type. By 6 months of age, the former showed a 30 percent drop in NAD⁺ and by one year, 45 percent. P7C3-A20 treatment normalized NAD⁺ levels at both time points.

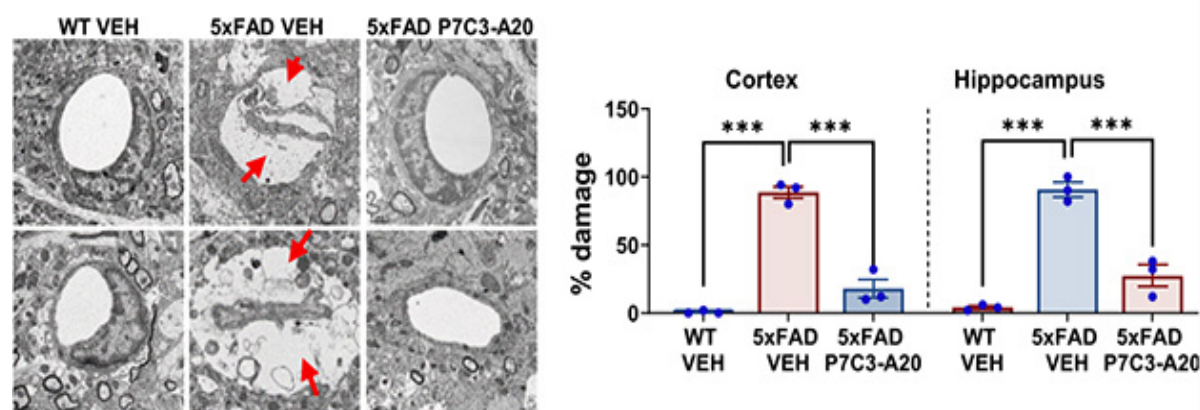
“P7C3-A20 safely stabilizes NAD⁺ homeostasis without elevating it to supraphysiologic levels. This is an important distinction from the mechanism of over-the-counter NAD⁺ supplements, which directly drive NAD⁺ synthesis,” Pieper wrote to Alzforum. Excessive NAD⁺ levels have been linked to numerous side effects, including cancer (Palmer and Vaccarezza, 2021).

With P7C3-A20 treatment, total A β peptide did not change—as APP cleavage is independent of NAD⁺—but thioflavin-S staining of aggregated amyloid was reduced in treated mice (image below). In mid-disease, the drug did not alter the amount of total or phosphorylated tau, but it lowered phospho-tau in advanced-stage mice, with no change in total tau. P7C3-A20 affected neither A β nor tau in wild-type mice.



Plaque Preventor. Thioflavin-S staining (magenta) of 12-month-old wild-type (left column) and 5xFAD (right column) mice; P7C3-A20 treatment (bottom row) led to fewer plaques in the cortices (left graph) and hippocampi (right graph) of AD mice. [Courtesy of Chaubey et al., *Cell Reports Medicine*, 2026.]

The scientists report that NAD⁺ restoration had other effects, as well. It repaired the blood-brain barrier, eased astrocytic and microglial inflammation, and shrank the number of DNA strand breaks. It preserved hippocampal long-term potentiation, a readout of synaptic health, in both mid- and advanced-disease stage 5xFAD mice.



More NAD⁺, Better BBB. Transmission electron microscopy of 12-month-old mouse cortices (top row) and hippocampi (bottom row) revealed wide gaps around vessels, a sign of barrier deterioration (red arrows), in 5xFAD vehicle-treated but not P7C3-A20 treated mice. [Courtesy of Chaubey et al., *Cell Reports Medicine*, 2026.]

The list goes on. For mice treated months 6 to 12, P7C3-A20 put the brake on neuronal death, as measured by immunofluorescence of the neuron-specific marker NeuN. In this age group, more newly generated hippocampal neurons survived, as per BrdU labeling. Tyrosine nitration and protein carbonylation, signs of metabolic stress, were up in both age groups of 5xFAD mice compared to wild-type; P7C3-A20 prevented and reversed this.

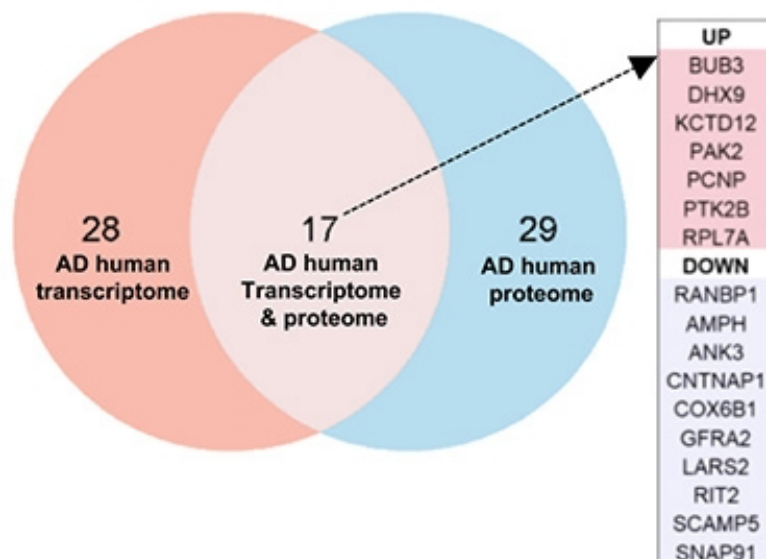
These biological changes came with behavioral benefits. Mice treated from months 6 to 12 outperformed controls in a battery of tests for memory, learning, and anxiety.

The researchers found no sex-specific differences. Nowadays, most research groups consider sex as a variable in preclinical mouse studies, with some opting to use only the sex in which their observed effect is strongest (Miller et al., 2017).

To explore how NAD⁺ restoration might work so broadly, the authors ran mass spectrometry proteomics of hippocampi from 1-year-old wild-type and 5xFAD mice. They found 174 proteins whose levels differed in the latter but were restored to normal by P7C3-A20. Comparing these with human AD brain proteome datasets, they saw that 46 were altered in the same direction in people with AD, and were also normalized in treated mice, highlighting conserved disease pathways. These 46 clustered into mitochondrial function, proteostasis, lipid handling, and immune signaling pathways.

A subset of 17 proteins also showed matching changes at the transcriptional level in AD human brains (image below).

Making a point about resilience, the authors report that brain samples of people who remained cognitively healthy despite extensive AD pathology showed expression of NAD⁺-consuming enzymes similar to controls—and higher than in symptomatic AD.



Gregory Brewer, University of California Irvine, called age-associated metabolic decline the “elephant in the room.” He wrote to Alzforum that the AD field has been distracted by large genomic datasets that reflect downstream changes but do not reveal true upstream disease triggers. Without interventional studies like this, he wrote, it is difficult to distinguish disease byproducts from drivers (comment below).

Proteomic Priorities. Of the 46 proteins whose directional changes aligned in mice and humans with AD, and responded to P7C3-A20 in mice (right circle), 17 also overlapped at the mRNA level in humans (middle). Seven proteins were upregulated and 10 downregulated in people with AD.

[Courtesy of Chaubey et al., Cell Reports Medicine, 2026.]

This drug's promise held up in a second model, the **PS19 tauopathy mouse**. Chaubey and colleagues injected P7C3-A20 at 11 months of age, near the end of this strain's lifespan of about one year, and claim that it improved scores on cognitive performance tests, bolstered BBB integrity, and protected against DNA damage.

“Of course, the next step is a human trial,” Pieper told Alzforum. To do that, he co-founded Glengary Brain Health in Cleveland.

According to Pieper, future clinical trials, which are some years away, will show whether restoring brain NAD⁺ homeostasis is sufficient to achieve disease recovery, either by itself or complementary to other available therapies.

For Swerdlow, these results reignite the question of whether there is a point of no return for AD treatment. “To me, there is no definitive evidence that there is a time beyond which we can no longer intervene,” he said to Alzforum. “The real challenge is finding what we need to fix.”

In line with this, Pieper told Alzforum his team is currently exploring the intersection between their mouse models and findings from human AD brains to identify which processes best complement NAD⁺-homeostasis-based recovery from disease.—Anna Bright

Anna Bright is a Ph.D. student in New York City.

COMMENTS



Gregory Brewer

UC Irvine, MIND Institute and Center for Neuroscience of Memory

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A paradigm shift for Alzheimer's pathogenesis and treatment?

For over a century, AD research has focused on amyloid and tau pathology, the big abnormal objects in the brains of dementia patients, and more recently on their systemic biomarkers. Now, in a large body of evidence, Chaubey et al. jump to the front of the pathogenic cascade by identifying an age- and pathology-dependent decrease in the NAD⁺/NADH redox ratio in two mouse models of AD. Disruptive to the dogma that degenerative diseases are irreversible, their pharmacological restoration of youthful NAD⁺/NADH reversed many of the biomarkers seen in AD mouse models along with cognitive restoration. Four months of daily intraperitoneal injections of P7C3-A20 restored NAD⁺/NADH levels in the 5xFAD mouse model at 12 months.

Remarkably, hippocampal LTP and novel object recognition were restored, thioflavin S A β plaques (but not 6E10) were lowered, along with p-tau in mouse brains and plasma. Leakage through the blood-brain barrier was tightened, and brain markers of inflammation were reduced. All this was caused by a drug that activates nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the salvage pathway to boost NAD⁺ levels.

Pieper's group work targeting the age-related decline in NAD⁺ levels supports our recent work in primary neurons from the 3xTg-AD model targeting NAD⁺ levels ([Santana et al., 2025](#)). Instead of drugging the enzyme, we treated neurons from old mice for just 24 hours with the substrate nicotinamide and the Nrf2-inducer EGCG. We showed rapid clearance of intraneuronal A β , lower oxidative protein nitration, and improved survival through a mechanism of rapid autophagic clearance.

It may be useful to reflect on reasons why the field didn't target the elephant in the room of declining energy levels with age affecting the brain. First, besides the strong support of the amyloid hypothesis, support for therapeutic reversal remains elusive. This may be just a self-fulfilling prophecy that AD is irreversible. Second, the large datasets generated from GWAS and transcriptional studies have generated hundreds of potential targets but they remain poor sources for identifying upstream control mechanisms.

Although Pieper's group attempts to reconcile mouse and human data by highlighting 17 transcriptome and proteome changes common to mice and human brains, this retrospective remains subject to the caveats of focusing on more abundant signals that could be downstream from less abundant but critical control points. Without interventions like those conducted by Pieper's group, we don't know which of these gene products are neuroprotective or pathologic.

Chaubey et al. admit the limitations of their reliance on familial mouse models of AD. Nicely mitigating this concern is the effectiveness of their P7C3-A20 in protecting human brain microvascular endothelial cells from oxidative stress.

Lastly, accurate measures of NAD⁺/NADH are notoriously difficult to come by, due to their metabolic dependence. The agonal state for mouse brain, and especially human postmortem samples, surely affect these measures, even though the authors were able to acquire reproducible values. We look forward to seeing the path to human translation for P7C3-A20 and the end to Alzheimer's as an irreversible disease.

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Evandro Fei Fang-Stavem

University of Oslo

Posted: 26 Jan 2026

These discoveries are in line with the very early studies and hypothesis from the Vilhelm Bohr and Evandro Fang labs, which have showed the benefits of NAD⁺ augmentation in neuronal resilience ([Fang et al., 2014](#)) and in slowing down pathologies in AD preclinical model systems ([Fang et al., 2019](#)).

NAD⁺ is an essential metabolite in life and health and is involved in a broad spectrum of metabolic (such as glycolysis, TCA, beta-oxidation, and OXPHOS) and cellular (such as substrate or co-enzymes for Sirtuins and PARPs) pathways ([Lautrup et al., 2019](#)). However, how NAD⁺ maintains neuronal resilience is still largely unknown. Known mechanisms including the stimulation of both macroautophagy ([Lee et al., 2008](#)) and mitophagy ([Fang et al., 2014](#); [Fang et al., 2019](#)). New studies from our group show that NAD⁺ restores proteostasis in AD through splicing-dependent autophagy via regulating EVA1C ([Ai and Fang, 2025](#); [Ai et al., 2025](#)) as well as regulates the splicing of the key neuronal protective protein REST (to be online in Brain soon, now accepted, [Lagartos-Donate et al.](#)).

Our group has highlighted the NAD⁺-mitophagy axis in AD inhibition. Now, there are several NAD⁺-based clinical trials for AD and PD (see our summary in Nature Ageing, [Zhang et al., 2025](#)), and we are now running a Phase 2 clinical trial on the use of a mitophagy inducer urolithin A to treat AD supported by the Alzheimer's Association ([Akershus](#)

[universitetssykehus HF, 2025](#)). For the current study, it would be so exciting to see a Phase 2 clinical trial in using P7C3-20 for AD (maybe not only MCI but late-state AD, as the authors claim REVERSAL).

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FURTHER READING

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[Could Disposing of Damaged Mitochondria Treat Alzheimer's Disease?](#) 15 Feb 2019

[An Axon Self-Destruct Button Triggers Energy Woes](#) 24 Apr 2015

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