Unlocking Brain Potential: Introducing 4-Hydroxybenzoate (4-HB) as a Revolutionary CoQ10 Alternative

Conventional CoQ10 supplements have extremely poor brain bioavailability, limiting their efficacy for neurological and cognitive health.

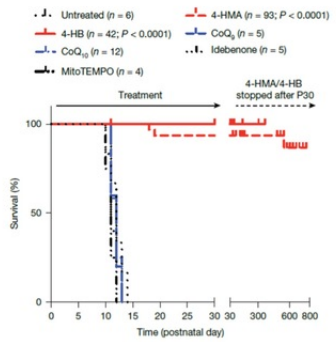

Figure 1. Oral supplementation of 4-HB (and 4-HMA; red lines) improves the overall survival for Hpdl-/- pups compared to supplementation with CoQ10, CoQ9, MitoTEMPO or Idebenone. 4-HB pups began treatment on P3-5.

Technology

NYU Langone Health researchers have uncovered the molecular building blocks of the lowly bioavailable CoQ10 enzyme, an important antioxidant that plays a crucial role in the production of energy within cells. 4-hydroxybenzoate (4-HB), a naturally occurring intermediate in the CoQ10 biosynthetic pathway, can bypass key transport bottlenecks and directly supplement CoQ10 synthesis in the brain. In a recent Nature study, orally administered 4-HB restored brain CoQ10 pools and improved neurological symptoms in *Hpdl*$^{-/-}$ mice, extending mouse pup survival to full adulthood, where mice treated with CoQ10 did not survive past postnatal day 15. (Figure 1.) Electrophysiological and histological improvements also confirm functional rescue of Purkinje cells in the cerebellum. In late 2023, 4 HB was supplemented in a pediatric patient with biallelic HPDL variants causing mitochondrial encephalopathy, under an FDA-approved single-patient IND. After 250 days of treatment, the patient showed stabilization of rapidly progressing spasticity as well as measurable improvements in motor function and physical endurance. This represents a compelling opportunity to develop 4-HB as a brain-targeted supplement for cognitive support, neurological aging, and overall mitochondrial health.

Background

Coenzyme Q10 (CoQ10) is a naturally occurring antioxidant found in the cells of the body, particularly within the mitochondria. It plays a crucial role in the production of adenosine

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triphosphate (ATP), which is the primary energy currency of cells. CoQ10 is an essential component of the electron transport chain, vital for the proper functioning of various organs and tissues, particularly those with high-energy demands, such as the heart, liver, and muscles. In addition to its role in energy production, CoQ10 also acts as an antioxidant, helping to protect cells from damage caused by free radicals. By neutralizing these reactive molecules, CoQ10 helps prevent oxidative stress, which can lead to cellular damage and contribute to aging and various diseases. The global CoQ10 supplements market exceeds $1.1B USD, driven by widespread use for cardiovascular, metabolic, and neurological support. However, CoQ10 given in supplements has extremely low levels of bioavailability, due to its large molecular size for BBB penetration. By supplementing small-molecule 4-HB, issues related to BBB penetration and CoQ10 bioavailability are overcome.

Development Stage

NYU is looking for partners that would like to develop therapeutics in the mitochondrial encephalopathy space and non-pharmaceutical supplements.

Applications

- **Cognitive health:** Brain-targeted CoQ10 elevation for aging, stress, and memory
- **Energy and mitochondrial function**: Supports ATP production and antioxidant defense
- **Neurological wellness:** Non-pharmaceutical support for neurological function

Advantages

- **Superior brain bioavailability** versus CoQ10
- **Endogenous pathway activation:** supplementing 4-HB as CoQ10 headgroup precursor
- **Natural compound** (<200 Da) suitable for consumer formulation
- **Proven safety** in preclinical and human use (under FDA single-patient IND)

Intellectual Property

NYU has filed multiple patent applications covering the methods of use, treatment and composition of matter.

References

1. Shi, G., Miller, C., Kuno, S. et al. , https://doi.org/10.1038/s41586-025-09246-x