4-Hydroxybenzoate (4-HB): A Next-Generation Brain-Bioavailable CoQ10 Alternative

Technology

Dr. Michael Pacold and Dr. Robert Banh at NYU Langone Health have developed a novel therapeutic approach using 4-hydroxybenzoate (4-HB), a small-molecule intermediate in the CoQ10 biosynthesis pathway, to restore endogenous CoQ10 production in patients with HPDL mutations. Published in *Nature* (July 2025), their work demonstrated that oral 4-HB dramatically increased brain CoQ10 levels, reversed neurological dysfunction in HPDL-deficient mice, and rescued over 90% of animals from perinatal lethality. This therapy has been validated through robust preclinical models and compassionate-use clinical experience in a single patient. In mice, 4-HB restored brain CoQ biosynthesis, reversed cerebellar degeneration, normalized electrophysiological activity in Purkinje neurons, and prevented death. In a pediatric patient with rapidly progressing HPDL-related spasticity, 4-HB treatment was well tolerated over >250 days and led to measurable neurological improvements, including enhanced mobility and reduced spasticity. Together, these findings establish 4-HB as a first-in-class, CNS-penetrant metabolite replacement therapy capable of addressing primary mitochondrial CoQ10 deficiencies.

Background

CoQ10 is essential for mitochondrial energy production and antioxidant defense. While CoQ10 deficiency syndromes are rare, they are often severe and present early in life with neurological and metabolic symptoms. Oral CoQ10 supplements fail to address brain deficiency due to poor CNS bioavailability. HPDL mutations result in a lethal infantile encephalopathy known as NEDSWMA (neurodevelopmental disorder with spasticity and white matter abnormalities), for which there is no approved treatment. The success of 4-HB in crossing the blood–brain barrier and being incorporated into endogenous CoQ offers a groundbreaking therapeutic strategy for a clearly defined, genetically stratifiable patient population.

Development Stage

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

Applications

Technology ID

PAC02-01-2

Category

Life Sciences/Therapeutics/Metabolic Diseases

Jane Liew/Amit Duvshani

Life Sciences/Therapeutics/Neurodeg Diseases

Sofia Bakogianni

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- **Monogenic mitochondrial encephalopathy:** HPDL-related primary CoQ10 deficiency (NEDSWMA).
- **Pediatric neurology:** Treatment of early-onset spasticity and neurodegeneration caused by genetic CoQ10 biosynthesis defects.
- **Rare disease therapy:** Orphan drug development pathway for ultra-rare mitochondrial and neurometabolic disorders.
- **Expanded therapeutic indications:** Potential for broader application in common conditions where traditional CoQ10 supplementation has shown limited clinical benefit.

Advantages

- **CNS-targeted therapeutic:** Crosses the blood–brain barrier and restores brain CoQ10 levels.
- **First-in-class mechanism**: Replaces upstream CoQ10 precursors rather than supplementing CoQ10 directly.
- **Demonstrated *in vivo* efficacy:** Rescues survival, motor function, and cerebellar structure in Hpdl / mice.
- **Human proof-of-concept:** Data in a pediatric patient under FDA IND.
- **Genetically stratified population:** Enables precision medicine trials in defined HPDL-mutant cohorts.

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://www.nature.com/articles/s41586-025-09246-x