Quinomics Assessment Reveals That BPM31510 Increases The Q Pool in Preclinical Mouse Models of Primary CoQ Deficiency That Present With Encephalopathy or Nephropathy

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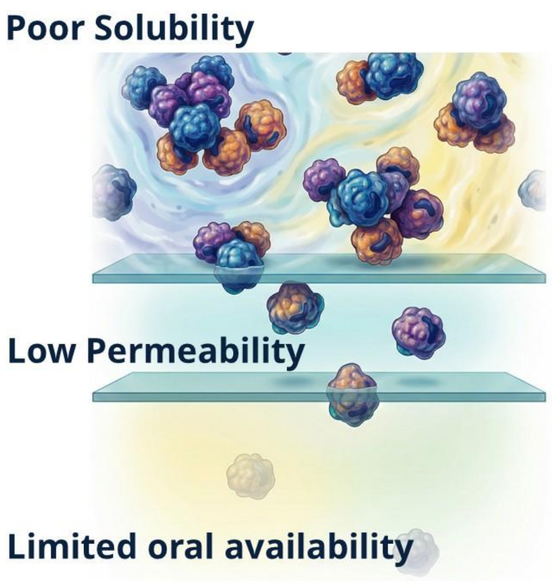
ABSTRACT

Primary Coenzyme Q10 deficiency (PCQD) is a rare mitochondrial disorder caused by mutations in CoQ biosynthetic genes. It typically presents as a clinically heterogenous disorder, most commonly manifesting as encephalopathy and nephropathy. The resulting decrease in tissue CoQ levels impairs mitochondrial function, leading to altered metabolism and increased ROS production. Additionally, reduction in CoQ levels can impact several other CoQ-interacting enzymes, altogether resulting in a complex metabolic disorder. In this study, we investigated the efficacy of BPM31510 – a lipid nanoparticle containing oxidized CoQ10 designed to enhance CoQ10 bioavailability and tissue delivery – in two distinct mouse models of PCQD: Coq9(R239X) (encephalopathy) and Pdss2$^{kd/kd}$ mice (nephropathy). Coq9(R239X) mice received intraperitoneal (IP) doses twice a week for two months, starting at post natal day 21 (onset of neurological pathology). Pdss2$^{kd/kd}$ mice were treated with the same IP regimen starting at 3 months of age (onset of renal pathology). Spatial and LC MS/MS quinomics and metabolomics are being utilized to assess broad changes in metabolism due to BPM31510 treatment in PCQD preclinical models. BPM31510 treatment increased the CoQ pool in the brain of Coq9(R239X) mice as well as in regions of the kidney in Pdss2$^{kd/kd}$ mice. The efficacy of BPM31510 in mitigating mitochondrial metabolic defects and restoring the function of CoQ-interacting enzymes is currently under investigation. Furthermore, neurological assessment utilizing the rotarod and pole test is also being investigated in BPM31510-treated Coq9(R239X) mice, while assessment of kidney function via proteinuria analysis in urine has already demonstrated improved renal function in BPM31510-treated Pdss2$^{kd/kd}$ mice. Altogether, these results demonstrate that BPM31510 treatment increased CoQ pool across tissues of affected organs with preliminary data suggesting improvement in phenotypic presentation in two pathologically distinct PCQD preclinical models. Moreover, spatial and LC MS/MS quinomics and metabolomics are actively being deployed to comprehensively characterize the metabolic changes associated with restoring the CoQ levels in these preclinical PCQD mouse models to guide the development of BPM31510 treatment in human clinical trials for PCQD.

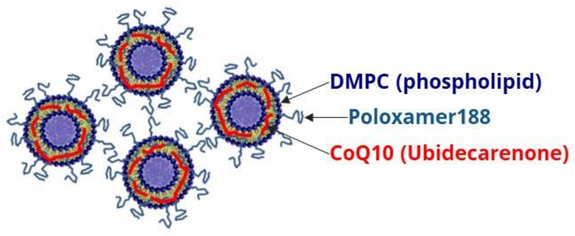
CHALLENGES FOR COQ10 THERAPEUTIC DEVELOPMENT

- Poor oral bioavailability (<0.1%)
- Lack of pharmaceutical cGMP grade product/formulations for IV, subQ, topical, or oral formulations
- Low PK/PD ratios to effectuate mitochondrial function at tissue level
- A true lack of the translational potential of the molecule in mainstream medicine and pharmaceutical ecosystem



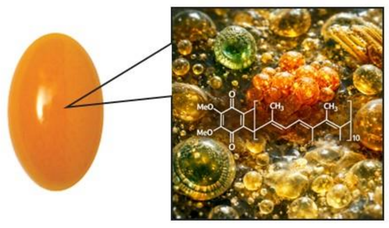
DEVELOPMENT OF A COQ10 LIPID NANODISPERSION (BPM31510)

BPM31510 (Lipid Nanosuspension Particle)



- Homogeneous lipid nanosuspension formulation
- Includes particle stabilizer at a proprietary and optimized ratio to lipids and ubiquinone
- Narrow 30-80 nm particle size
- Charge and size allow for cell and mitochondrial penetration
- Stable GMP IV formulation for therapeutic applications
- Crosses blood brain barrier

OTC Oral CoQ10 (Ubiquinol Mixture)



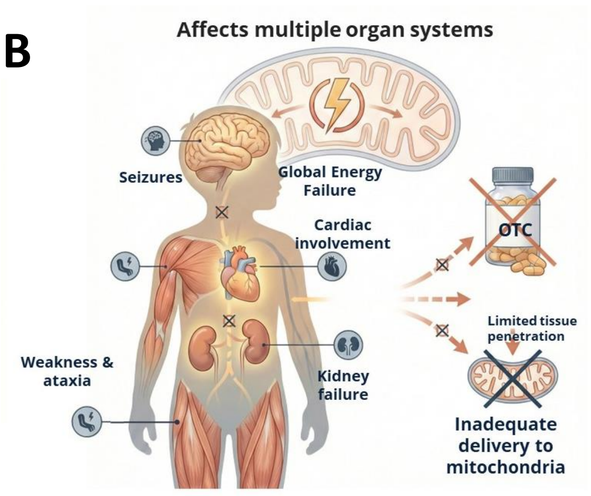
- Heterogeneous mixture of ubiquinol with consumer oils
- Large CoQ10 crystals ranging in size from 200-1000 nm are unstable and insoluble

PRIMARY COQ10 DEFICIENCY (PCQD) DISEASE BACKGROUND

A

- Caused by mutations in one or more genes involved in the biosynthesis of CoQ10
- Typically, neonatal to childhood age of onset
- Common outcome is serious disability or fatality
- The current standard of care is oral OTC CoQ10 that is ineffective

B



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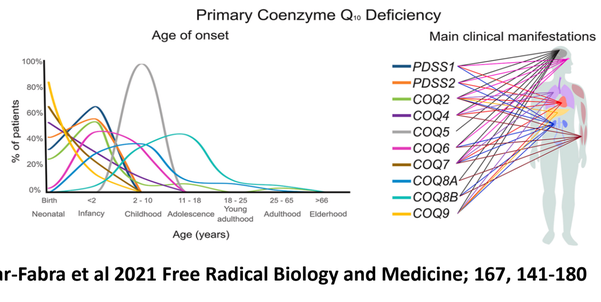

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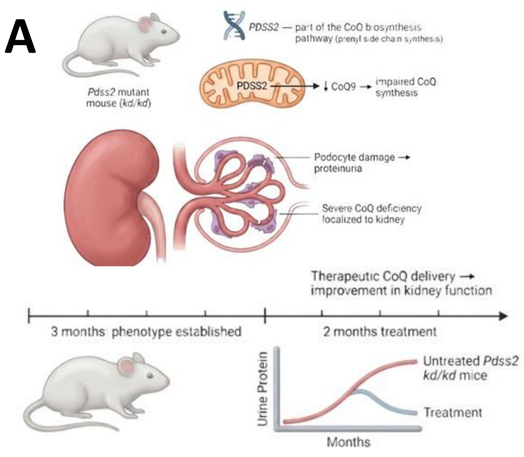
Figure 3: (A) and (B) Epidemiology and clinical presentation of PCQD. (C) Genetic linked age of onset based on mutational status.

BPM31510 TREATMENT OF Pdss2$^{kd/kd}$ MOUSE IMPROVES PROTEINURIA

A



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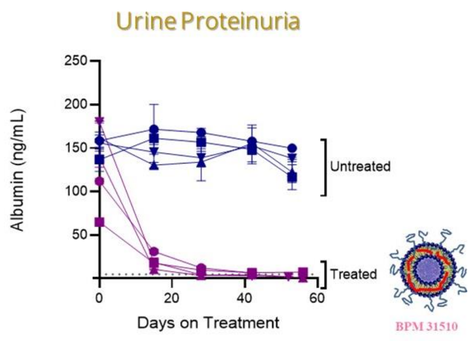

Figure 4: (A) Pdss2$^{kd/kd}$ BPM31510 treatment study design. (B) Assessment of proteinuria in Pdss2$^{kd/kd}$ with or without BPM31510 treatment.

BPM31510 TREATED Pdss2$^{kd/kd}$ KIDNEYS EXHIBIT METABOLIC CORRECTION

CoQ Spatial Distribution	• Restoration of CoQ levels in medulla as well as inner/outer cortex of the kidney
Pathology	• Clear improvement in kidney associated pathology
Citrate Levels	• Citrate levels returned to normal demonstrating unblockage of TCA cycle
ATP Levels	• Increase in ATP generation in BPM31510 treated mouse Pdss2$^{kd/kd}$ kidneys

Figure 5: Spatial quinomics quantified delivery of CoQ10 to the medulla and inner/outer cortex of BPM31510 treated kidneys. Spatial metabolomics also demonstrated a correction of citrate metabolism and increase in ATP production in Pdss2$^{kd/kd}$ kidney treated with BPM31510.

BPM31510 IMPROVES MITOCHONDRIAL FUNCTION IN Pdss2$^{kd/kd}$ KIDNEYS

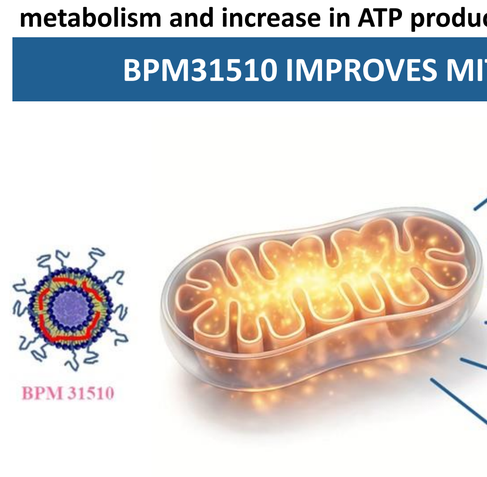

Figure 6: Summary of metabolic assessment of quinomics and spatial metabolomics in BPM31510 treated Pdss2$^{kd/kd}$ kidneys.

BPM31510 TREATMENT OF CoQ9^{R239X} MICE INCREASES Q POOL IN BRAIN

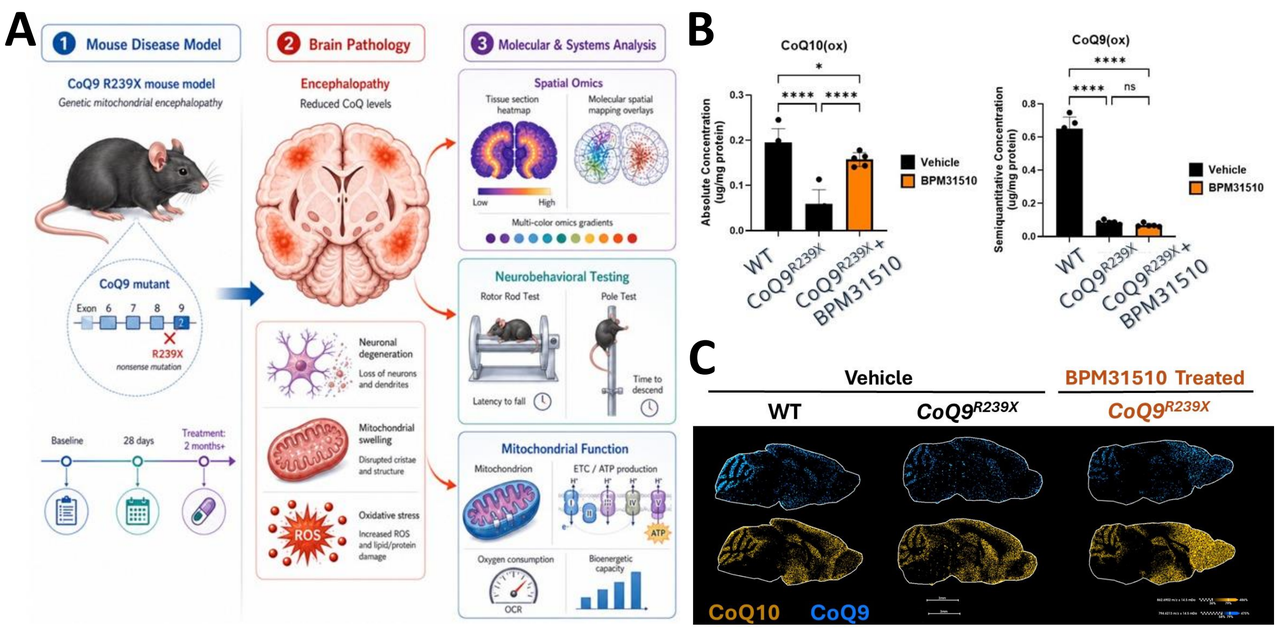

Figure 7: Coq9^{R239X} mice are treated with BPM31510 and assessment of mitochondrial function is ongoing. (B) High resolution LC MS/MS analysis of CoQ species demonstrates BPM31510 increased oxidized CoQ10 levels in treated CoQ9R239X brains, while endogenous CoQ9 species were unchanged. Spatial quinomics of mouse brains demonstrated corresponding spatial distribution of CoQ in BPM31510 treated mice.

CONCLUSIONS

- **BPM31510 rapidly improved proteinuria in Pdss2$^{kd/kd}$ mice following treatment.**
- **BPM31510 increases CoQ10 content in tissues and mitochondria,** as evident by biochemical correction and activity of known CoQ interacting pathways and functions within the mitochondria.
- **Crosses the blood brain barrier** as evident of quantitative quinomics and spatial quinomics assessment in an encephalopathy mouse model of PCQD.
- BPM31510 represents a potential therapeutic approach for the treatment of PCQD since it delivers CoQ10 to highly metabolic tissues and corrects metabolic dysfunction, warranting further investigation.

Disclaimer:
BPM31510 is an investigational drug.

BPM31510 has not been approved by the U.S. Food and Drug Administration (FDA) or any other regulatory authority. The safety and efficacy of BPM31510 have not been established by the FDA.

Information provided here is intended for scientific and educational purposes only and should not be construed as indicative of any therapeutic benefit.