BPM31510 Increases The CoQ Pool In Cerebellum As Assessed By Spatial Quinomics And Restores Kidney Function In Preclinical Models Of CoQ Deficiency

Michael A. Kiebish[1], Elliana Barriocanal-Casado[2], Sylwia A. Stopka[1], Alba Pesini[2], Juan J. Aristizabal-Henao[1], Srada Karmacharya[1], Devon Van Cura[1], Ryan Zhang[1], Kelsey R. Nickerson[1], Kashni Grover[1], Oksana Zavidij[1], Sarah R. Wessel[1], Niven R. Narain[1,3], Vijay Modur[1], Stephane Gesta[1], Catarina M. Quinzii[1]

[1]BPGbio, Waltham, MA USA, [2]Columbia University New York, NY USA, [3]Departments of Dermatology & Cutaneous Surgery and Biochemistry and Molecular Biology, Miller School of Medicine, University of Miami, Miami, FL USA,

ABSTRACT

Introduction: Primary Coenzyme Q10 (CoQ_{10}) deficiency (PCQD) is a rare mitochondrial disorder caused by mutations in genes involved in CoQ biosynthesis (e.g., *COQ4, PDSS2*). The resulting decrease in mitochondrial CoQ levels impairs electron transport chain activity, leading to defective mitochondrial respiration, increased oxidative stress, and dysfunction across high-energy–demand tissues such as brain, heart, kidney, and skeletal muscle. PCQD is clinically heterogenous, but two predominant phenotypes are commonly observed: progressive ataxia (driven by cerebellar metabolic abnormalities) and renal dysfunction. Although oral CoQ_{10} supplementation has been investigated clinically, its therapeutic impact is limited by poor absorption and suboptimal tissue distribution, particularly to the CNS.

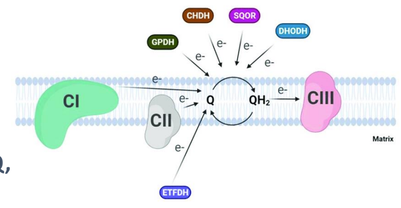
Methods: BPM31510 is a lipid nanoparticle formulation of oxidized CoQ_{10} designed to enhance bioavailability and tissue delivery. In the current study, we assessed the ability of BPM31510 to increase CoQ levels in *Coq4*^{F147C} mice, a novel genetic knock-in model for PCQD, as well as *Pdss2*$^{kd/kd}$ mice, utilizing a mass spectrometry platform that leveraged both targeted LC-MS/MS and spatially resolved MALDI-MSI.

Results: BPM31510 treatment significantly increased oxidized CoQ_{10} levels across multiple tissues, most importantly the cerebellum and kidney. MALDI-MSI revealed regional and spatial increases of CoQ_{10} within the brain, particularly within the cerebellum. Spatial quinomic analysis further demonstrated increased level of CoQ_{10} in the molecular and granular layers as well as the fiber tracts of the cerebellum in BPM31510-treated PCQD models. In the kidney, BPM31510 enhanced oxidized CoQ_{10} levels in the outer cortex, medulla, and pelvis regions of BPM31510-treated PCQD animal models, as assessed by spatial quinomics. Importantly, in the *Pdss2*$^{kd/kd}$ mouse model, BPM31510 treatment led to resolution of proteinuria at 3 months of age, within just two weeks of therapy.

Conclusion: These preclinical studies highlight the translational potential of BPM31510 treatment, demonstrating enhanced spatial delivery of CoQ10 and improvements in disease-relevant measures characteristic of PCQD pathophysiology, supporting further investigation.

FIGURE 1: CoQ10 and Challenges of Developing CoQ10 as a Therapeutic

CoQ10 plays an integral role in mitochondrial metabolism, ROS generation, and maintaining the electron gradient



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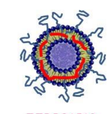
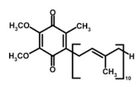
Challenges in Development of CoQ10 as a Therapy

- 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

FIGURE 2: Development of BPM31510 For Delivery of Supraphysiological Concentrations of CoQ10





- Proprietary & **stable** formulation
- Contains **CoQ10** and nanoparticle lipid membrane to modify mitochondrial metabolism
- A **bio-membrane** -like capsule
- Enrichment in **mitochondria**
- Well-tolerated with a **favorable safety profile**

FIGURE 3: BPM31510 Treatment Of A *Coq4*^{F147C} Mouse Model

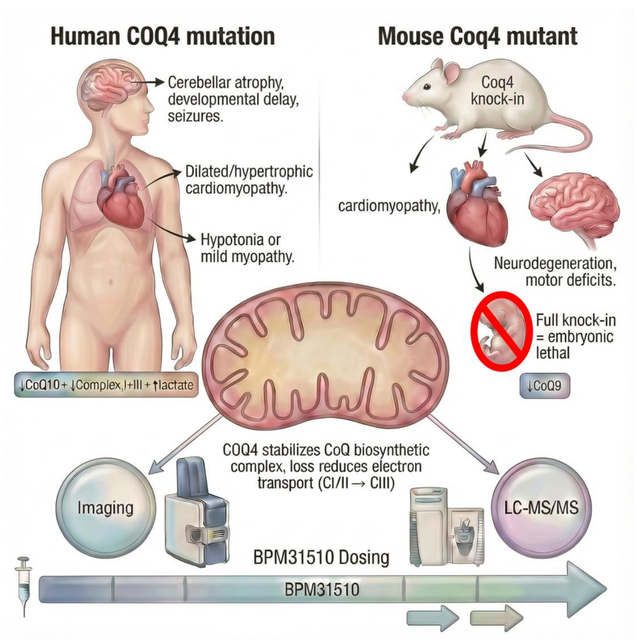
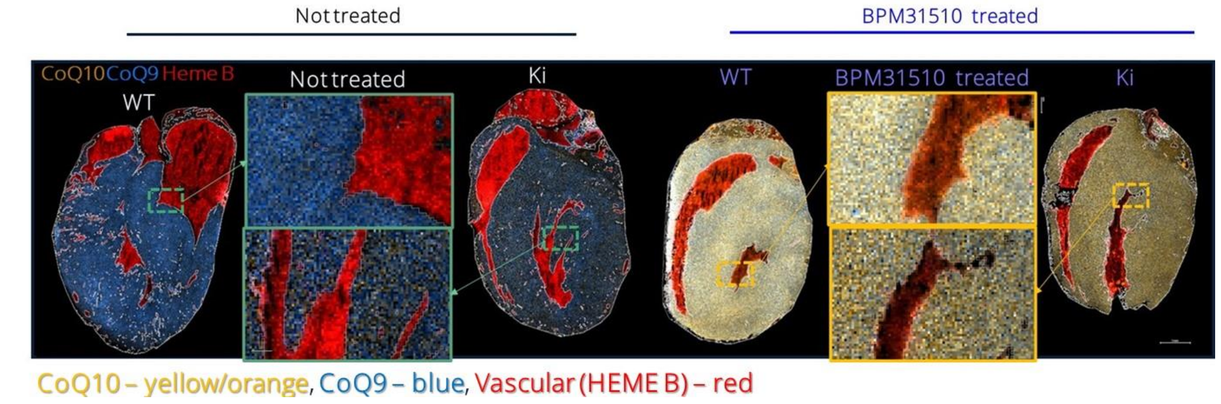


Figure 3: In humans, COQ4 mutations present as a neurological, muscular and cardiac condition due to CoQ10 deficiency. A *Coq4*^{F147C} mutant mouse model was generated leading to CoQ deficiency across tissues. To evaluate delivery of CoQ10 through BPM31510 treatment, we treated mice for two weeks followed by evaluating CoQ10 levels spatially across key tissues involved in CoQ10 deficiency pathogenesis (i.e. brain- most notably cerebellum for ataxia, heart, and kidney). A spatial MALDI-MSI quinomics workflow was developed spraying deuterated CoQ10 onto tissue and measuring single cell levels of CoQ levels across tissues to assess delivery of CoQ10 from BPM31510.

FIGURE 4: BPM31510 Delivers CoQ10 To The Brain, Most Notably Cerebellar Regions

Figure 4: MALDI-MSI spatial quinomic assessment of wildtype and *Coq4*^{F147C} mouse sagittal brains revealed quantitative increases in CoQ10 delivery with BPM31510 across specific brain regions as identified by CoQ10 quantitation (orange). Further segmentation of cerebellar regions (molecular and granular layers along with fiber tracts) revealed significant increase of CoQ10 delivery from BPM31510 treatment across cerebellar subregions demonstrating an increase in the CoQ pool of *Coq4*^{F147C} *treated mice*.

FIGURE 5: BPM31510 Delivers CoQ10 Throughout Myocardium of *Coq4*^{F147C} Mutant Mice Increasing the Q Pool



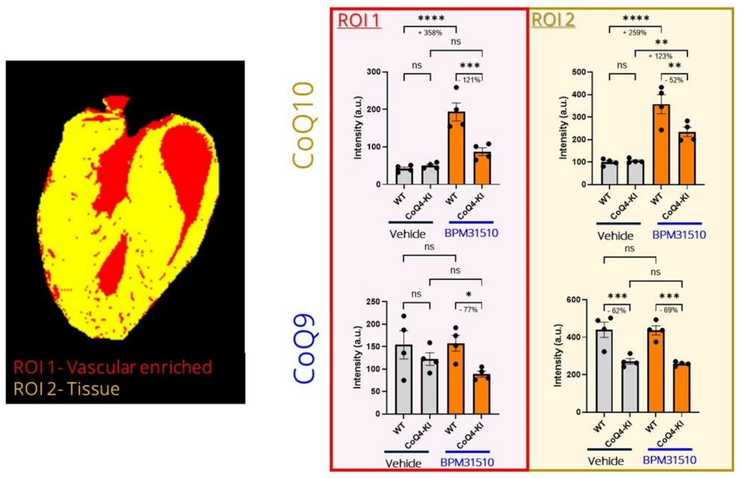


Figure 5: Cardiac function is commonly affected in PCQD and even more so in mitochondrial diseases in general. To assess cardiac delivery of CoQ10 by BPM31510, we evaluated cardiac tissue in WT and *Coq4*^{F147C} mice using MALDI-MSI quinomics which revealed significant increase of CoQ10 throughout cardiomyocytes. This delivery statistically increased the overall CoQ10 pool in the myocardium.

FIGURE 6: BPM31510 Delivers CoQ10 Throughout Kidney Regions of *Coq4*^{F147C} Mutant Mice Increasing the Q Pool

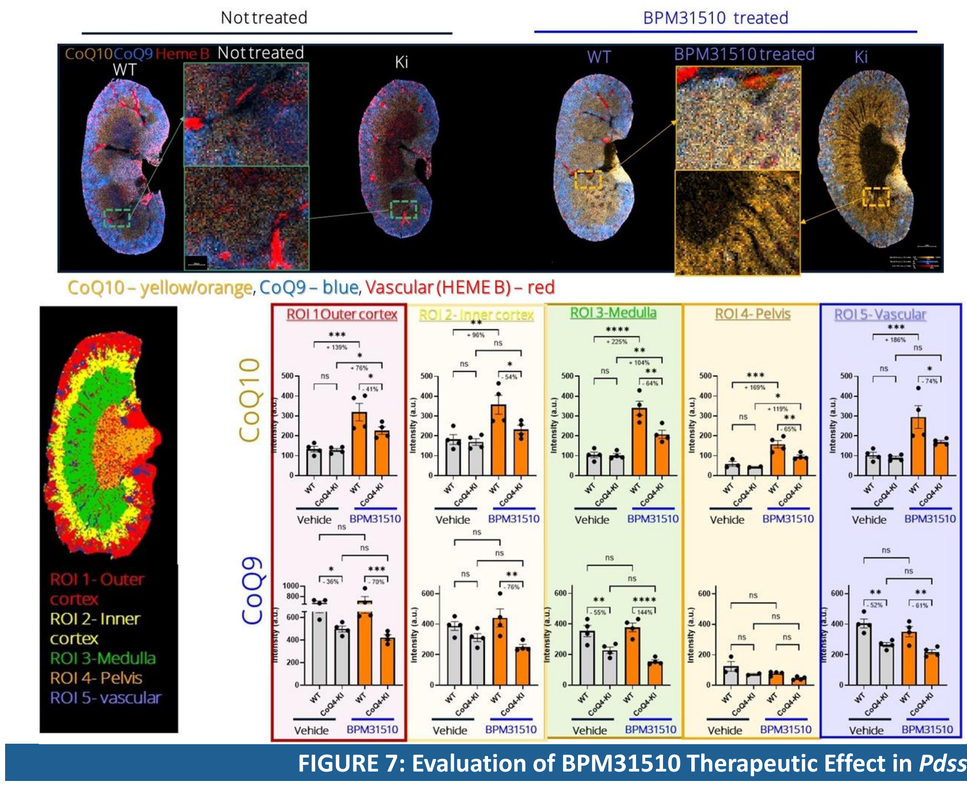
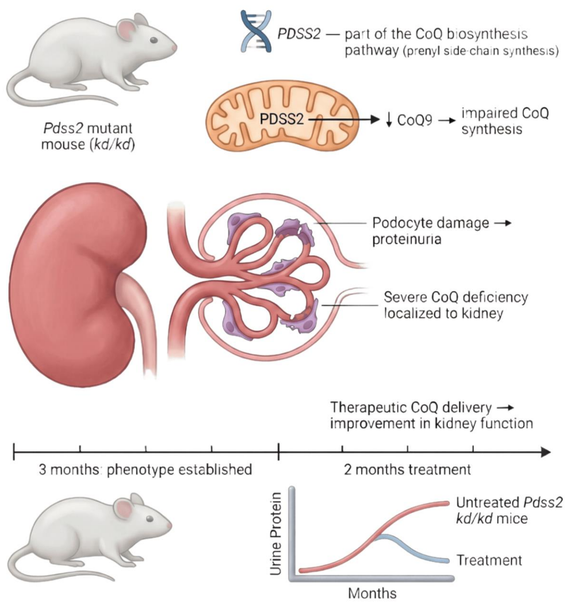


Figure 6: Renal dysfunction is a common clinical presentation in PCQD and mitochondrial diseases. To assess delivery of CoQ10 throughout renal subcompartments (outer cortex, inner cortex, medulla, pelvis, and vascular regions) we performed MALDI-MSI quinomics on WT and *Coq4*^{F147C} mutant untreated and BPM31510 treated mice. BPM31510 demonstrated increased delivery of CoQ10 across kidney subcompartments increasing the CoQ pool within the tissue subregions. This suggests potential broad functional activity throughout the kidney.

FIGURE 7: Evaluation of BPM31510 Therapeutic Effect in *Pdss2*$^{kd/kd}$ Mice



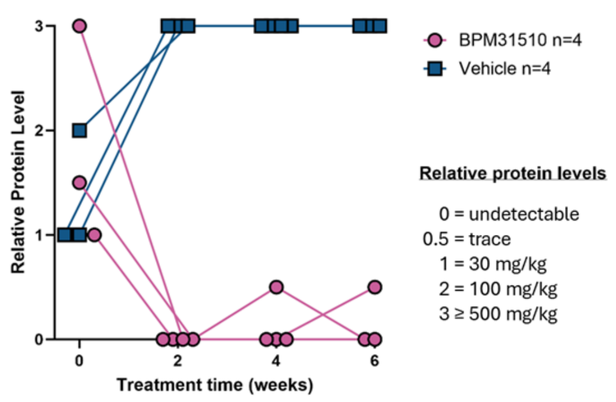
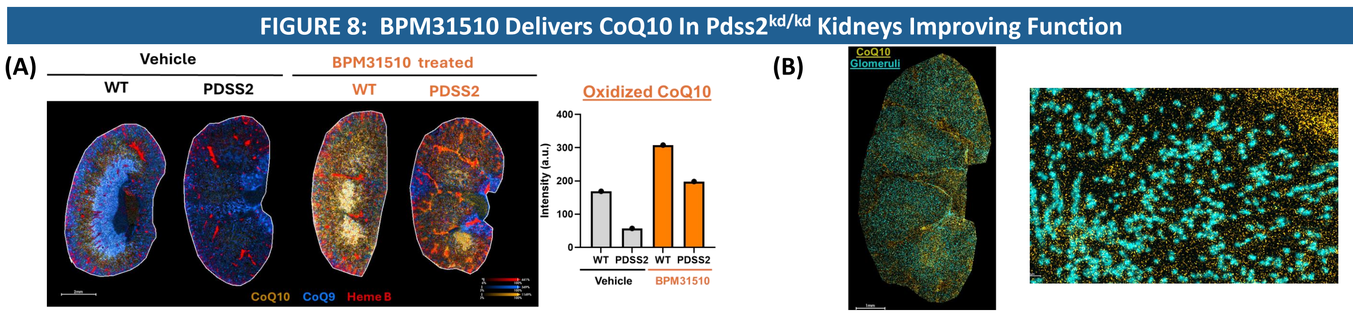


Figure 7: *Pdss2*$^{kd/kd}$ mice exhibit a dominant nephrotic dysfunctional phenotype due to abnormalities in kidney CoQ levels demonstrating a progressive increase in proteinuria. *Pdss2*$^{kd/kd}$ mice were treated at 3 months of age (an age where clear kidney pathology is exhibited) with BPM31510 to evaluate kidney CoQ10 levels, pathology, and subsequent effect on proteinuria for the course of 2 months of BPM31510 treatment.

FIGURE 8: BPM31510 Delivers CoQ10 In Pdss2$^{kd/kd}$ Kidneys Improving Function



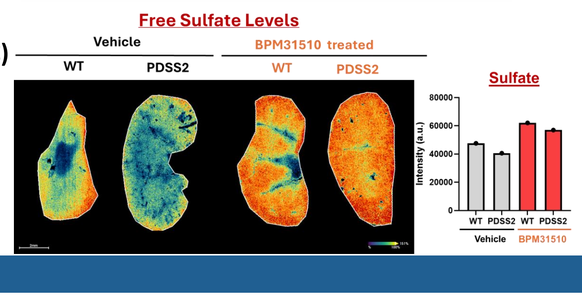


Figure 8: BPM31510 increased kidney CoQ10 levels in WT and *Pdss2*$^{kd/kd}$ mice (A). Further, BPM31510 delivered CoQ10 to the tubules and glomeruli, most notably the tubule regions which are the most mitochondrial rich in *Pdss2*$^{kd/kd}$ mice (B). Initial investigation evaluating metabolites impacted by CoQ activity revealed an increase in free sulfate levels in BPM31510 treated WT and *Pdss2*$^{kd/kd}$ mice (C).

CONCLUSIONS

- **BPM31510 was investigated in two independent preclinical models of PCQD to evaluate restoration of CoQ pool in multiple tissues impact by primary CoQ deficiency.**
- **BPM31510 treatment in a *Coq4*^{F147C} mouse model demonstrated a statistical increase of CoQ10 in brain, cerebellum, and cerebellar subregions in treated mice increasing the overall CoQ pool as well as the ability of BPM31510 to cross the blood brain barrier. Further, BPM31510 was able to increase CoQ pool throughout the myocardium along with several subregions of kidney in the *Coq4*^{F147C} mouse model as determined by MALDI-MSI spatial quinomics.**
- **Treatment of BPM31510 in *Pdss2*$^{kd/kd}$ mice revealed an improvement of proteinuria as well as increase in the CoQ pool and sulfate generation in the kidney of treated mice as determined by MALDI-MSI spatial omics.**
- **In summary, BPM31510 was able to increase the CoQ pool in PCQD preclinical models overcoming major hurdles in the therapeutic development of CoQ10.**