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Presenter: Peter J. Oates

Authors: Peter J. Oates[1], James Carr[1]

Institution: [1]Stealth Biotherapeutics Inc., 275 Grove Street, Newton, MA 02466

Title: Urinary Metabolite Changes and Correlations with Six Minute Walk Test Distance in Elamipretide-treated Subjects with Mitochondrial Disease in the MMPOWER Trial

Body of Abstract:

INTRODUCTION: SPIMM-201 was a multi-center, randomized, double-blind, three-dose-ascending, placebo (PCBO)-controlled study of once-a-day elamipretide (ELAM) for 5 days in 36 subjects with genetically confirmed primary mitochondrial myopathy (PMM). The study demonstrated a dose-dependent (P=0.014) increase in six-minute-walk distance (6MWD), P=0.0297. Exploratory data on selected urinary metabolites from SPIMM-201, their correlations and some possible implications for PMM are now presented. **METHODS:** Three first-morning-void (FMV) urines were collected: day 1 (baseline; first 6MWD prior to drug), day 5 (*prior to* last ELAM dose, second 6MWD) and day 7. The UCSD Biochemical Genetics and Metabolomics Laboratory analyzed 294 metabolites in 106 of 108 intended urine samples. Metabolites were normalized to creatinine and internal standards. Data were log-transformed, filtered using interquartile ranges and analyzed by traditional univariate approaches and by nonparametric methods with non-log-transformed data. **RESULTS:** After 4 days of ELAM, urinary creatinine, pyruvate, lactate and Krebs cycle intermediates were unchanged from baselines. ELAM dose-dependently lowered the aggregate Day 5-Day 1 change in 20 amino acids (AA) from +22% in PCBO to -12% in the high dose ELAM group (HD) (P=0.0003, ANOVA). ELAM treatment showed dose-dependent lowering of isoleucine from +34% rise in PCBO to -14% in HD (P=0.0001 ANOVA); of leucine from +32% rise in PCBO to -17% in HD (P = 0.0023); of urea cycle intermediates ornithine from +56% in PCBO to -19% in HD (P=0.0041) and arginine from +157% in PCBO to -27% in HD (P=0.012), findings all consistent with a reduction of proteolysis. The HD group had ~30-55% decreases in C_6-C_9 dicarboxylic acids (DCA), e.g., adipic acid -37% (P=0.023 vs. 0 (0=no change)), suggesting reduced microsomal fatty acid ω-oxidation and peroxisomal β-oxidation. These observations were reinforced by correlation analyses: changes in HD group ornithine (r_S=0.883, P=0.0031 (uncorrected for multiple comparisons)) and adipic acid (r_S=0.767, P=0.021) correlated more strongly with changes in 6MWD than other AAs or DCAs examined. Finally, in the HD group, on a *per subject* basis, decreases in ornithine (urea cycle catalyst) and in adipic acid (product of peroxisomal DCA β-oxidation) strongly correlated (r_S=0.933, P=0.0007) with one another, a finding suggesting a quantitatively coordinate downshift in resting proteolysis and fatty acid oxidation after 4 days of ELAM. **CONCLUSIONS:** These exploratory findings are consistent with the hypothesis that in PMM although high intra-mitochondrial NADH typically impedes Krebs cycle metabolism and mitochondrial β-oxidation of fatty acids, energetic impairment can be partially compensated by 1) robust glycolytic metabolism largely disconnected from mitochondrial metabolism, 2) proteolysis with muscle metabolism of isoleucine and related AAs to succinyl-CoA (“bypassing” dysfunctional Complex I / elevated mitochondrial NADH), and 3) ω-oxidation of medium chain fatty acids in the endoplasmic reticulum to DCAs, followed by peroxisomal β-oxidation of longer DCAs to adipic and succinic acids to support mitochondrial post-Complex I electron transfer. These exploratory data further suggest a working hypothesis that after 4-5 days of HD ELAM PMM subjects had improved mitochondrial bioenergetic efficiency as evidenced not only by increased 6MWD, but also by coordinated decreases in resting rates of proteolysis and microsomal/peroxisomal fatty acid oxidation.