A Novel Small-Molecule PPARδ Modulator for the Treatment of Fatty Acid Oxidation Disorders

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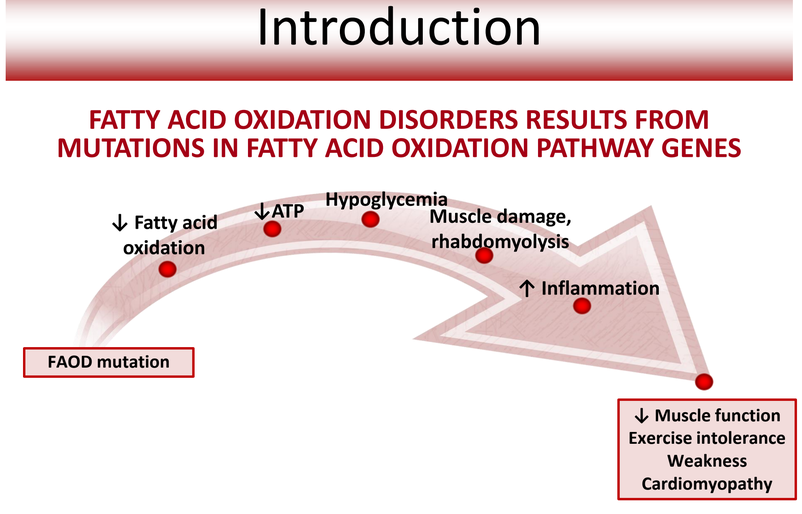
Abstract

Fatty acid oxidation disorders (FAODs) are a heterogeneous group of inborn errors of metabolism that are characterized by reduced metabolic flexibility leading to hypoglycemia, reduced exercise tolerance, and multi-organ dysfunction. They are caused by mutations in metabolism-related genes, including those coding for key enzymes of the fatty acid β-oxidation cycle, which lead to reduced fatty acid metabolism. MA-0211 (*a.k.a.* MTB-1) is a novel, orally-available, small molecule currently in a Phase 1 clinical study that modulates PPARδ, a key nuclear hormone receptor which regulates cellular metabolic flexibility. Administration of MA-0211 in multiple animal models has demonstrated significant improvements in several FAOD related manifestations, such as increasing exercise endurance, protecting against cardiac dysfunction and acute kidney injury. In the present report, we evaluated whether MA-0211 can improve fatty acid oxidation in fibroblasts derived from patients with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. The results show that MA-0211 increases VLCAD mRNA, protein levels, and enzymatic activity in a dose responsive manner. MA-0211 increases utilization of palmitate and changes the acyl-carnitine profile in a manner consistent with increased long-chain fatty acid oxidation in patient cells that are expected to have some residual enzymatic activity based on their mutation. Additionally, improvements in fatty acid oxidation were observed in patient fibroblasts derived from long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and mitochondrial trifunctional protein (TFP) deficiency. In conclusion, the significant improvements seen in FAOD patient fibroblasts together with previous demonstrations of *in vivo* pharmacological activity, support studying MA-0211 in patients with FAODs.

Introduction

FATTY ACID OXIDATION DISORDERS RESULTS FROM MUTATIONS IN FATTY ACID OXIDATION PATHWAY GENES

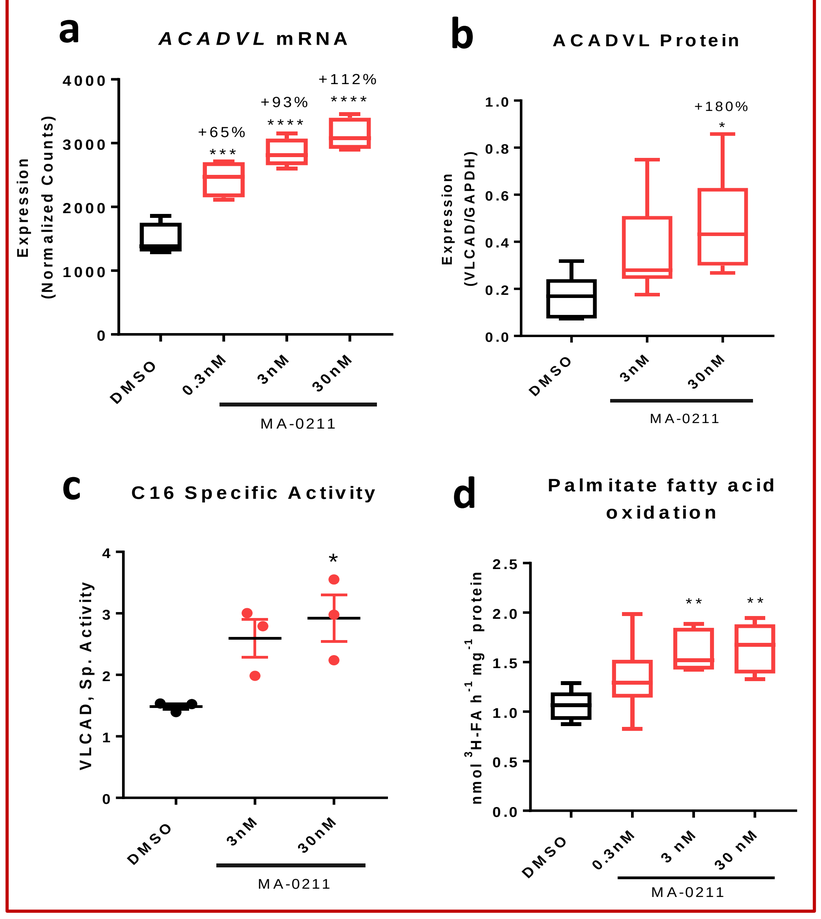


- MA-0211 was tested in a number of animal models with the following benefits:
  - ✓ Improved cellular FAO and ATP in multiple cell types
  - ✓ Protection from muscle damage
  - ✓ Increased endurance
  - ✓ Preservation of cardiac function
  - ✓ Protection from kidney injury
  - ✓ Reduction of inflammatory cytokines

Hypothesis: MA-0211 will increase long-chain fatty acid oxidation in fibroblasts derived FAOD patients by increasing the expression of the mutated gene and protein thereby increasing the residual enzymatic activity

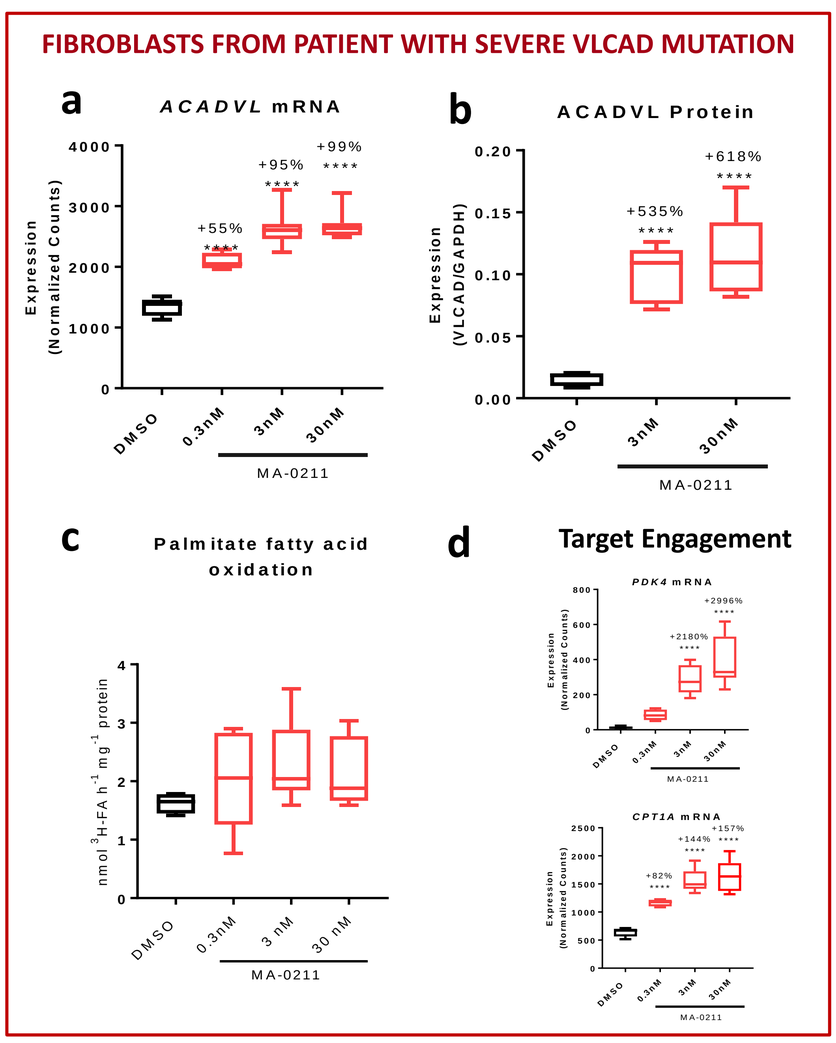
MA-0211: VLCAD patient derived fibroblasts

FIBROBLASTS FROM PATIENT WITH MILD VLCAD MUTATION



VLCAD cells: ACADVL heterozygote, Allele 1: V283A; Allele 2: A161V
*p<0.05, **p<0.01 ***p<0.001, ****p<0.0001; (a, b, d) One way ANOVA Dunnett's test .

FIBROBLASTS FROM PATIENT WITH SEVERE VLCAD MUTATION

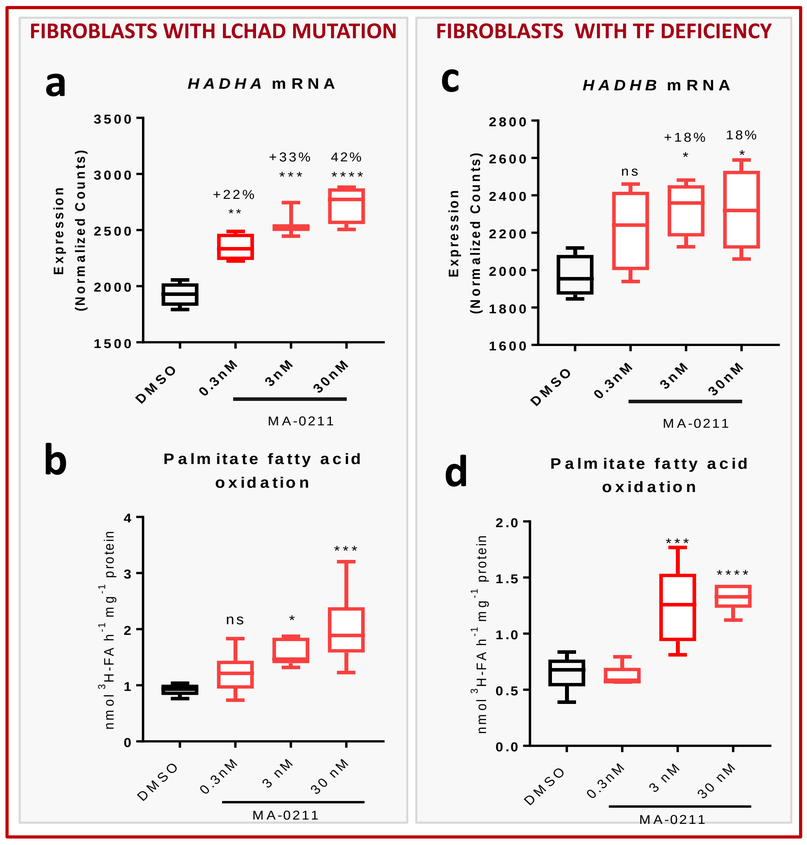


VLCAD cells: ACADVL heterozygote, Allele 1: I373T; Allele 2: R453Q
****p<0.0001; (a-c) One way ANOVA Dunnett's test

MA-0211: LCHAD and trifunctional deficient patient derived fibroblasts

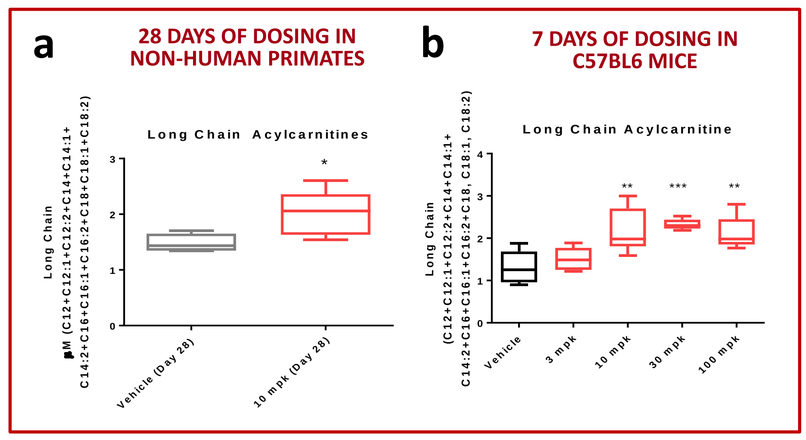
FIBROBLASTS WITH LCHAD MUTATION

FIBROBLASTS WITH TF DEFICIENCY



LCHAD cells: E510Q/E510Q (common mutation)
TFD cells: HADHB, G182A/G182A, R28H
*p<0.05, **p<0.01 ***p<0.001, ****p<0.0001; (a, b, c, d) One-Way ANOVA Dunnett's test.

MA-0211: Acylcarnitines in healthy mice and non-human primates



*p<0.05, **p<0.01, ***p<0.00; 1 (a) unpaired two-tailed t-test (b) One-Way ANOVA Dunnett's test.

Conclusions

- MA-0211 is a potent and selective modulator of PPARδ that increases the expression of genes encoding proteins involved in fatty acid oxidation in fibroblasts from FAOD patients
- In VLCAD patient derived fibroblasts MA-0211 can increase FAO when there is sufficient residual protein present
- In vivo MA-211 has shown benefits in a variety of disease models such as mdx, DIO, AKI and increased long chain acylcarnitines in healthy mice and non-human primates
- MA-0211 is currently in Phase 1 studies for Duchenne Muscular Dystrophy in partnership with Astellas Pharma

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