

A Novel Drug Therapy Strategy for Treating Fatty Acid beta-Oxidation Disorders

"Inborn errors of metabolism resulting in accumulation of harmful metabolites can be lethal or cause irreversible brain damage during episodes of metabolic decompensation, especially when the deficiency is severe and medical attention is delayed. Current therapies are ineffective in preventing the life threatening symptoms caused by beta-oxidation deficiencies. While milder presentations can result from a low level of enzyme activity that is preserved, defective enzymes in cells are typically present in low amounts and are often unstable and prone to breakdown, especially when exposed to higher temperatures as during fever with illness. Stability of abnormal enzymes can often be partially prevented by binding of specific small molecules known as ligands to the enzyme. Among the most potent stabilizing ligands are an enzyme's own reaction substrate(s) or product(s), but only if they are present at appropriate concentrations. Because substrates/products are already in situ, they have an advantage over exogenous "chaperone" ligands that often need to be administered to patients at high concentrations risking harmful side effects.

We treated cells from patients with various beta-oxidation defects including medium chain acyl-CoA dehydrogenase, very long chain acyl-CoA dehydrogenase, long chain 3-hydroxyacyl-CoA dehydrogenase, and trifunctional protein deficiencies with trimetazidine at doses significantly lower than those prescribed in Europe and elsewhere to treat ischemic heart disease. Trimetazidine inhibits the final reaction in the fatty acid beta-oxidation cycle, and thus it has the potential to increase cycle intermediates in cells that may act as endogenous chaperonins to stabilize mutant enzymes. Our laboratory studies confirmed a significant increase in mutant proteins detected in patients' cell lines along with an increase in activities of upstream reactions, providing proof of concept of this novel drug targeting approach.

We believe that trimetazidine can address an unmet need in these diseases. Moreover, we have additional preliminary data in patient cells that demonstrate that trimetazidine can work synergistically in combination with other drugs, multiplying the potential effectiveness of trimetazidine. While we predict that the late onset patients of beta-oxidation disorders will benefit clinically the most from our drug therapy strategy, patients with early onset are likely to see improvement as well."

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