



Department of Pharmaceutical Sciences
Ph.D. Dissertation Defense Seminar

Friday, March 17, 2023
10:00 am

Rackham Building, West Conference Room - Fourth Floor
Zoom: <https://umich.zoom.us/j/93840644387>

“L-carnitine as a Probe to Assess Mitochondrial Drug Toxicity”

Presented by:



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Abstract: Despite ongoing scientific advancements adverse drug reactions (ADRs) continue to pose significant challenges for patients and the healthcare system. Some ADRs have been associated with off-target drug interactions with mitochondria. Recently, mitochondrial metabolites have become of interest because of their potential use as signaling molecules for mitochondrial health. This dissertation focused on identifying mitochondria-specific metabolites that could be clinically used to probe and assess drug-induced mitochondrial related alterations in metabolism. For this, we employed a database screening strategy with an *a priori* established criteria which identified L-carnitine as a candidate mitochondrial metabolite that could be useful for identifying individuals at increased risk of mitochondrial-related ADRs. Growing evidence revealed the potential use of L-carnitine and acetylcarnitine as mitochondrial biomarkers of ADRs, beyond their current use to screen neonates for inborn errors of metabolism. We hypothesized that changes in L-carnitine disposition, induced by a “challenge test” of intravenous L-carnitine, could identify mitochondrial related ADRs by provoking variation in L-carnitine and/or acetylcarnitine blood levels. To test this, we used an established animal model of mitochondrial drug toxicity in which male C57BL/6 mice were treated with clofazimine (CFZ) by its addition to their chow for 8-weeks. Following CFZ treatment, mice were injected with a high dose (1,000 mg/kg) of L-carnitine, “challenge test”. The L-carnitine “challenge test” identified CFZ-dependent differences in whole blood acetylcarnitine concentration. This finding supports and substantiates the potential of the “challenge test” as a probe to identify drug-related toxicological manifestations. To further establish L-carnitine feasibility for clinical use in both male and female, and to aid in further closing the knowledge gap of sex-related differences in ADR incidence, we conducted the L-carnitine “challenge test” in male and female mice and measured additional whole blood metabolite concentrations using nuclear magnetic resonance (NMR). L-carnitine-induced similar differences in whole blood acetylcarnitine concentration in both male and female CFZ-treated mice, indicating no apparent sex-related differences in mitochondrial metabolism related to long-term CFZ treatment. Although CFZ treated male and female mice exhibited similar levels of measured whole blood metabolites, these levels varied significantly within the same sex. This finding suggests that metabolomics could lead to better understanding of the mechanisms/pathways that are affected and may contribute to ADRs. Overall, this dissertation provided evidence to support that clinical use of an L-carnitine challenge test with subsequent measurement of mitochondrial metabolites like acetylcarnitine, could be an important early step to identify occult medication-induced mitochondrial toxicity.