COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar Series

Hybrid

Wednesday, January 25, 2023
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Zoom

"Identifying Endogenous Candidate Metabolites to Probe and Assess Mitochondrial Drug Toxicity"

Presented by:

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Abstract: Adverse drug reactions (ADRs) are considered an inherent risk of medication use, and some ADRs have been associated with off-target drug interactions with mitochondria. Metabolites that reflect mitochondrial function may help identify patients at risk of mitochondrial toxicity. We employed a database screening strategy to identify candidate mitochondrial metabolites that could be clinically useful to identify individuals at increased risk of mitochondrial-related ADRs. L-carnitine, its acetylated metabolite, acetylcarnitine and other acylcarnitines are mitochondrial biomarkers used to detect 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 hypothesis, we induced mitochondrial drug toxicity with clofazimine (CFZ) in a mouse model. Following CFZ treatment, mice received an L-carnitine "challenge test". CFZ-induced changes in weight were consistent with previous work and reflect CFZ induced catabolism. L-carnitine induced differences in whole blood acetylcarnitine concentrations in a manner that was dependent on CFZ treatment. This supports the usefulness of a database strategy for the discovery of candidate metabolite biomarkers of drug toxicity and substantiates the potential of the L-carnitine "challenge test" as a "probe" to identify drug-related toxicological manifestations.