COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Department of Pharmaceutical Sciences
Ph.D. Dissertation Defense Seminar

Monday, April 10, 2023
10:00am
Michigan League, Vandenberg (2nd floor)
Zoom Details: https://umich.zoom.us/j/5503684400
Meeting ID: 550 368 4400 / Passcode: 284698

"Mechanistic Analysis and Quantification of Clofazimine"

Presented by:

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Abstract: In drug therapy, knowledge of the mechanism of drug distribution is important because it can inform the origins of adverse drug reactions (ADRs) that can result from high concentrations of drug in specific tissues. To this end, we conducted a study of the Food and Drug Administration (FDA) approved drug, clofazimine (CFZ), a weakly basic, highly lipophilic drug that is known to bioaccumulate in macrophages of both humans and mice. By analyzing age-related, CFZ-induced changes in tissue composition, metabolic function, drug sequestration ability, and immune response, we can better understand the processes and risk factors that contribute to ADRs.

We focused our studies on the assessment of CFZ accumulation in a macrophage-rich drug sequestering organ (spleen), and skeletal muscle. Since ADRs are more prevalent in older individuals and skeletal muscle mass and function decline with age, we also investigated the impact of age on drug accumulation in the skeletal muscle. We used C57BL6 male mice, and after prolonged CFZ exposure, we isolated and weighed tissues to quantify the amount of drug and used microscopy techniques to detect drug within cells. Since CFZ targets macrophages, we conducted cytokine arrays to determine the cytokine signals associated with macrophage differentiation. We also modeled changes in muscle mass of mice treated with CFZ and performed functional tests to understand tissue structure ADRs over time. Additionally, since CFZ is known to disrupt mitochondrial function, we tested the utility of blood levels of the mitochondrial metabolites, L-carnitine and acetylcarnitine, to detect CFZ-induced ADRs.

Our results showed that spleen mass from CFZ-treated mice increased but its cargo capacity was maintained between young and old mice. However, the amount of CFZ and cargo capacity of skeletal muscle macrophages increased in old mice compared to young mice, even though muscle mass was lost with treatment. The cytokine signals of skeletal muscle from old CFZ-treated mice was consistent with that of diseased muscle, which was not evident in young mice. Mitochondrial metabolism, determined by the ratio of acetylcarnitine to L-carnitine was altered in old skeletal muscle but not in the blood.

In conclusion, our study highlights the impact of prolonged drug treatment and age on drug bioaccumulation in macrophage-rich tissues like the spleen and skeletal muscle. These findings emphasize the importance of understanding how drug distribution could potentially contribute to ADRs. Specifically, we found that the accumulation of CFZ led to an increase in spleen mass suggests a potential role in drug sequestration, and age-related changes in the muscle increase drug accumulation. These findings provide important insights that could direct future research to mitigate ADRs.