COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar Series
Hybrid

Wednesday, February 8, 2023
4:00pm
2548 NUB
Zoom

"Immune System Impacts on the Pharmacokinetics of Weak Bases"

Presented by:

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Abstract: Many weakly basic drug molecules accumulate in the body after repeated dosing leading to adverse events or long-term morbidity. The macrophage is a lucrative cell of the immune system implicated in many instances of bioaccumulation. Due to the endophagocytic role it occupies in maintaining homeostasis and its disseminated nature in biological systems, macrophages create a perfect environment for the accumulation of drug molecules. As a result, macrophages can induce "context-dependent" pharmacokinetics, or deviations from standard, concentration-dependent pharmacokinetics. This phenomenon can cause time, load, or dose-dependent alterations in drug distribution profiles at therapeutic doses. By examining pharmacokinetic impacts of the macrophage and macrophage storage sites, such as the spleen, we can develop more robust and reliable predictive analyses.

The FDA approved drug Clofazimine (CFZ), used in tuberculosis and leprosy, provides an exceptional experimental system to test the hypothesis of bioaccumulation as a mechanism underlying the context-dependent pharmacokinetics in weak bases. Under therapeutically relevant conditions, CFZ forms membrane-bound supramolecular crystal-like drug inclusions (CLDIs) within lysosomes of resident macrophages. Under daily dosing regimens, serum drug concentration remains constant while the organ-associated mass of drug continues to increase throughout the dosing duration. The pharmacokinetic analysis of CFZ within a single macrophage and macrophage containing organs can yield insights into the mechanistic underpinnings of cellular drug disposition, increasing half-life, and organ associated mass of the drug under constant administration. Integrating physiochemical knowledge of weakly basic molecules with whole body distribution patterns creates a framework for predicting context-dependent pharmacokinetic changes driven by the immune system. Utilizing this approach can directly point to optimal steady-state drug loading to reduce toxicity of exogenous drug molecules.