COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar

Wednesday, March 30, 2022
4:00pm
2548 NUB or Zoom

"Pharmacokinetic Analysis of Phase Transitions in Weakly Basic Accumulating Xenobiotics"

Presented by:

Andrew Willmer
Pharmaceutical Sciences, PhD Candidate

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 implicated in many of these 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 xenobiotic drug accumulation. 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 re-evaluating concentration-dependent steady state in the context of xenobiotic therapeutics causing and undergoing phase transitions, we can develop more robust and reliable pharmacokinetic 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 of weak bases. Under therapeutically relevant conditions, CFZ forms membrane-bound supramolecular crystal-like drug inclusions (CLDIs) within the lysosomal compartment 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. Preliminary findings indicate the context-dependent distribution of CLDIs *in vivo* can be predicted by a nonlinear, adaptive, drug load-dependent function. The resulting load-dependent analysis of CFZ 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 basic molecules with whole body distribution patterns creates a framework for predicting soluble-to-insoluble phase transitions. Utilizing this approach can directly point to optimal steady-state drug loading to reduce toxicity of xenobiotic molecules.

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