COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

The Pharmaceutical Sciences Department
is pleased to announce the
Ph.D. Dissertation Defense Seminar of

Phillip Rzeczycki
Pharmaceutical Sciences, Ph.D. Candidate
(Mentor: Dr. Gus Rosania)

Tuesday, December 19, 2017
2:00 pm
2548 C.C. Little Building

"The Role of Macrophages in the Sequestration of Drug and Formation of Insoluble Drug Aggregates"

Abstract: Drugs with poor aqueous solubility generally possess unfavorable pharmacokinetic properties. Upon oral administration, such drugs can form supersaturated solutions within the gastrointestinal tract, causing the formation of insoluble aggregates which may be prone to precipitate out in the body. Clofazimine, an oral leprostatic drug in clinical use since the 1960s, is known to massively bioaccumulate in the form of insoluble, crystal-like drug inclusions (CLDIs). These CLDIs are primarily found within tissue macrophages of the liver, spleen, and lungs. Here, we hypothesized that CLDIs are stabilized by an active, macrophage-dependent concentrative proton and chloride transport process. To test this, we developed a multi-parameter imaging and analysis system which combines polarization and fluorescence microscopy to track the accumulation and stabilization of CLDIs in different macrophage populations throughout treatment, revealing tissue-specific differences in the ability to stabilize intracellular drug aggregates, and an active remodeling of the internal arrangement of the macrophage's membranes to maximize drug loading. Additionally, following chemical depletion of macrophages in the liver and spleen, CLDI accumulation was significantly inhibited, resulting in a reduction in the total drug accumulation within the organs. Most importantly, depletion of hepatic macrophages alongside drug treatment caused liver damage and systemic toxicity, leading us to postulate that drug sequestration and subsequent granuloma formation by macrophages functions as a protective mechanism. When macrophage-depleted mice were injected with isolated CLDIs, there was a significant increase in the rate of decay of the crystals, indicating that phagocytosis by the macrophage stabilizes the crystal and prevents dissolution. Finally, we determined that CLDI-containing macrophages showed significantly higher levels TFEB activation, lysosomal content and autophagic flux, pointing to an active adaptation of the macrophages' endolysosomal system to accommodate and stabilize CLDIs. To conclude, macrophages are actively involved in sequestering drug and help to limit drug toxicity.

Defenses are open to the public.