

The sequestration of drugs in lysosomes: Mechanisms and therapeutic consequences



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Human cells have complex structure and contain numerous organelles and compartments that can house therapeutic targets and/or provide sites for extensive drug accumulation. For these reasons the intracellular disposition of drugs can impact both therapeutic activity and pharmacokinetic attributes. This presentation will begin with a general description of the major sites for drug accumulation in human cells and will then focus on our work in studying weakly basic drug accumulation in acidic organelles such as lysosomes according to an ion trapping-type mechanism. I will briefly highlight some of our past work centered on how structural and physical properties of drugs impact lysosomal accumulation. I will also describe our identification of a lysosomal protein named Niemann-Pick C1 that we have shown to play an important role in mediating lysosomal drug accumulation. The remainder of the presentation will be devoted to our work examining the potential impact of lysosomal trapping on therapeutic activity and pharmacokinetics. The end of the presentation will focus on some of our more recent studies investigating potential pharmacokinetic drug-drug interactions involving lysosomes.

Dr. Jeff Krise is currently an associate professor of pharmaceutical chemistry at the University of Kansas. He holds a Bachelor of Science degree in pharmacy from Duquesne University (1993). He earned his PhD (with honors) from the Department of Pharmaceutical Chemistry at the University of Kansas in 1998. Dr. Krise received postdoctoral training at Stanford University School of Medicine from 1998 to 2001 in the Department of Biochemistry. In 2001 he began his academic career at the University of North Carolina at Chapel Hill in the Division of Drug Delivery and Disposition. In 2004 he moved to back to the University of Kansas in the Department of Pharmaceutical Chemistry. His laboratory investigates how small molecular weight drugs distribute and localize in cells and how this influences therapeutic activity and toxicity.