Translational Approaches to Understand and Predict Rare Adverse Reactions to Drugs

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The Hamner – UNC
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Sciences

Recent true case

An FDA review of a New Drug Application supported the sponsor's conclusions that the drug was effective. However, it was noted that among ~4,000 patients treated in clinical trials, two patients developed elevations in liver chemistries possibly, but not definitely, indicating potential for liver toxicity.

This was not a first in class drug.

As a requisite for approval, the company was told to conduct a new safety study of 20,000 patients treated with drug or comparator for one year.

Concept of idiosyncratic adverse drug events

Major efforts to find and study people who have experienced rare SAEs

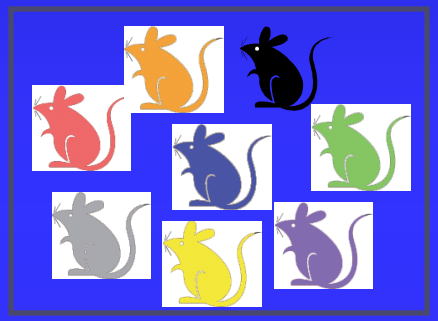
Severe Adverse Events Consortium

Drug-Induced Liver Injury Network
(NIDDK supported)

Challenge

How can we generate new hypotheses to test in these people and their tissues?

Using Panels of Inbred Mice to Identify Mechanisms of Idiosyncratic Toxicities

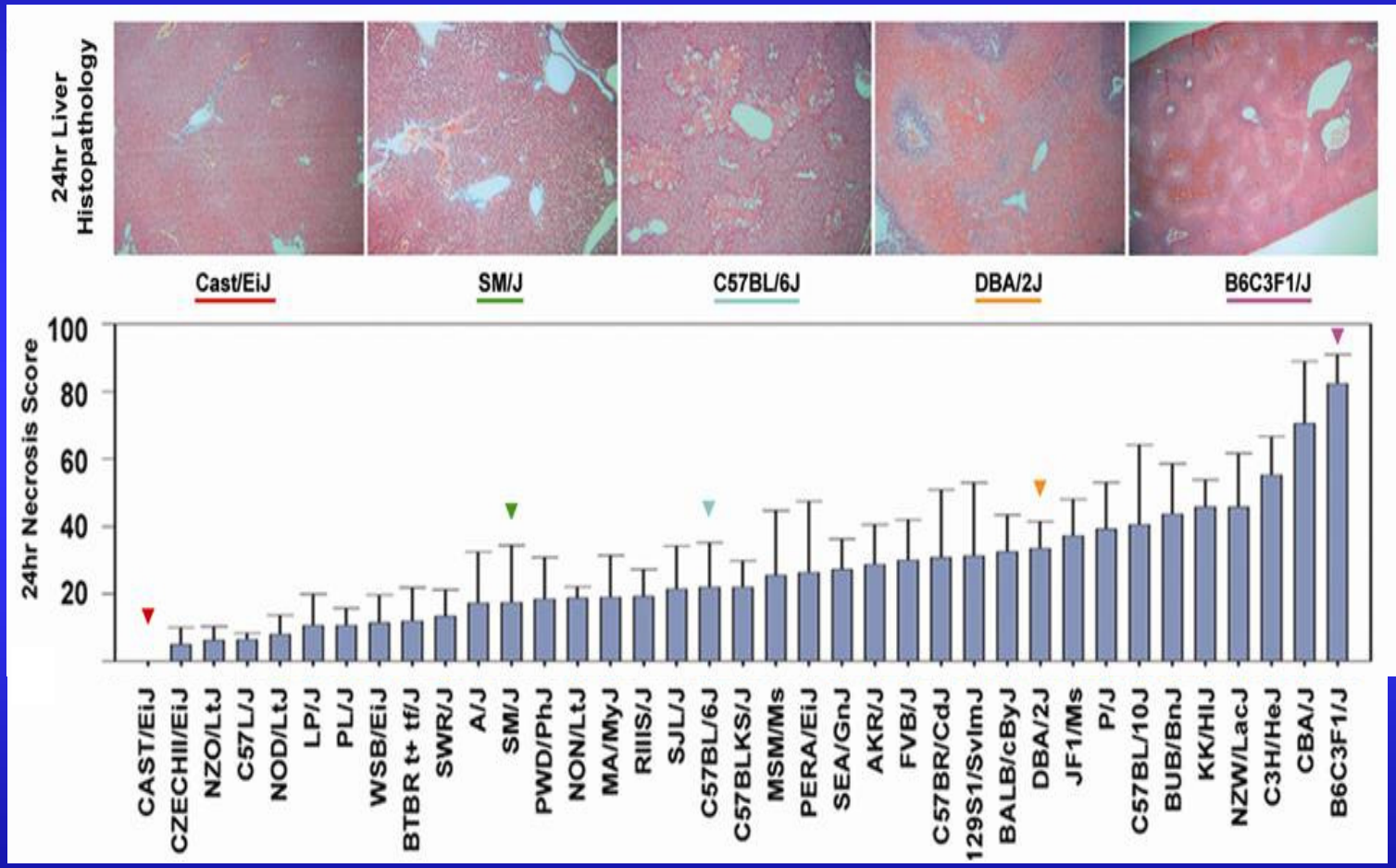


Genetically Diverse Mouse Population

NIH,1RC1DK087510-01
Title: Revolutionizing preclinical safety testing
PIs: Threadgill / Watkins

Acetaminophen liver Injury: 36 strains, 300 mg/kg (*i.g.*)

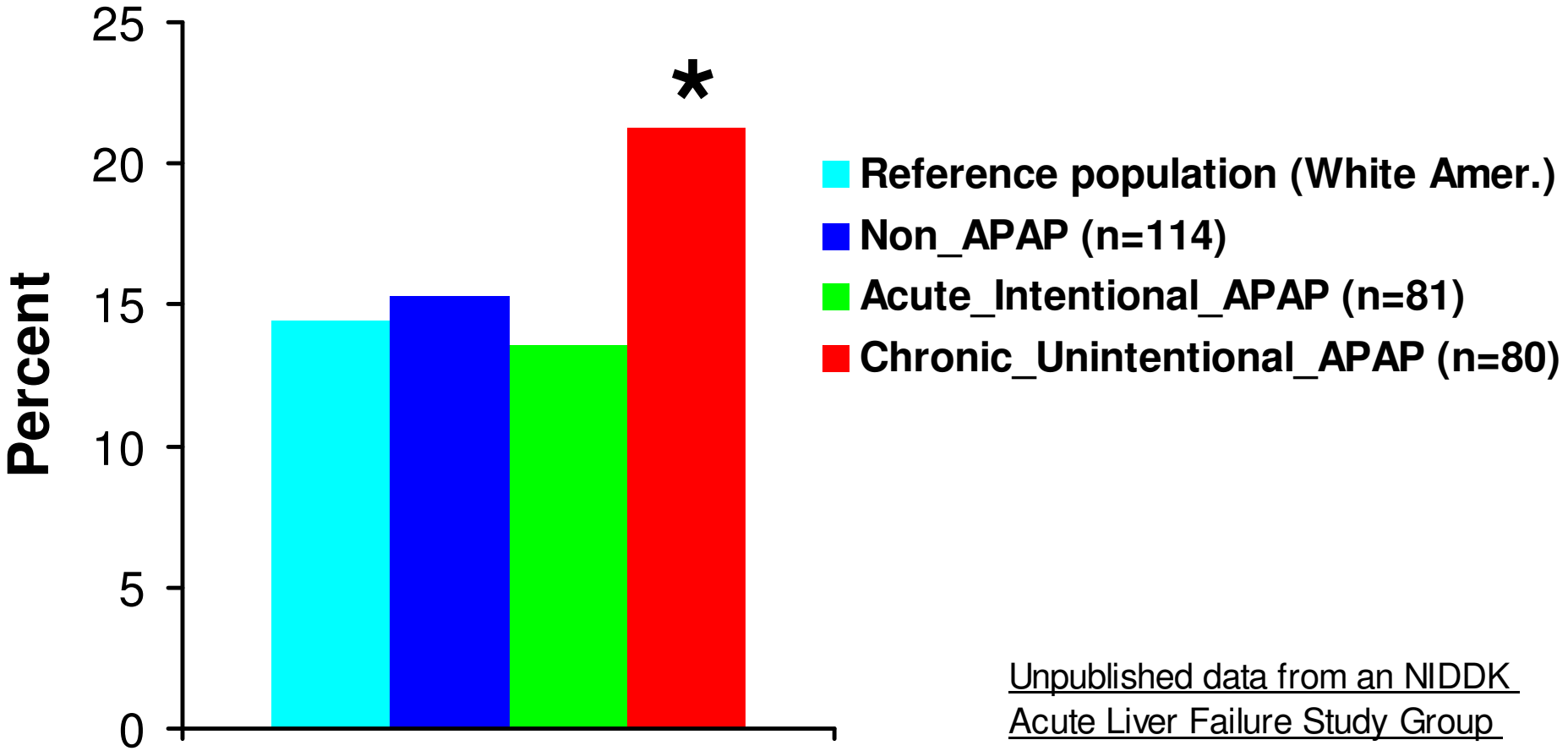
24 hr Necrosis



Inbred Mouse Strains

Genome Research, (9):1507-15, 2009

CD44 polymorphism (I497T) allele frequency in 275 white acute liver failure subjects



* P = 0.014 by Chi-squared test

Unpublished data from an NIDDK Acute Liver Failure Study Group ancillary study

P.I.- M.H. Court (Tufts University)

Co.I. - W.M. Lee (UTSW)

Drugs to be tested in the Collaborative Cross mice

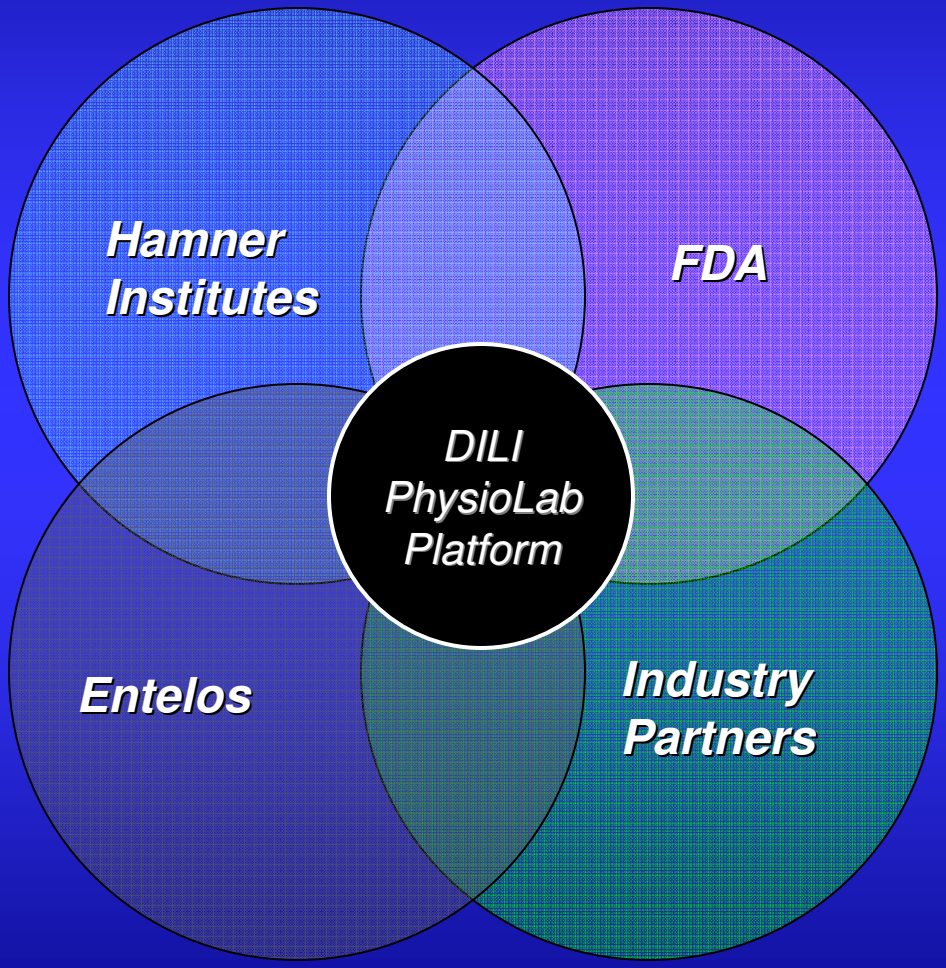
1). Drugs most frequently implicated in available genebanks (DILIN, Severe adverse Events Consortium)

2). Proprietary drugs that failed in man due to adverse events.

The Hamner-UNC Institute for Drug Safety Sciences

Entelos/FDA collaboration

DILI PhysioLab Platform Initiative
A Partnership Between Hamner Institutes, FDA, Entelos, and Industry



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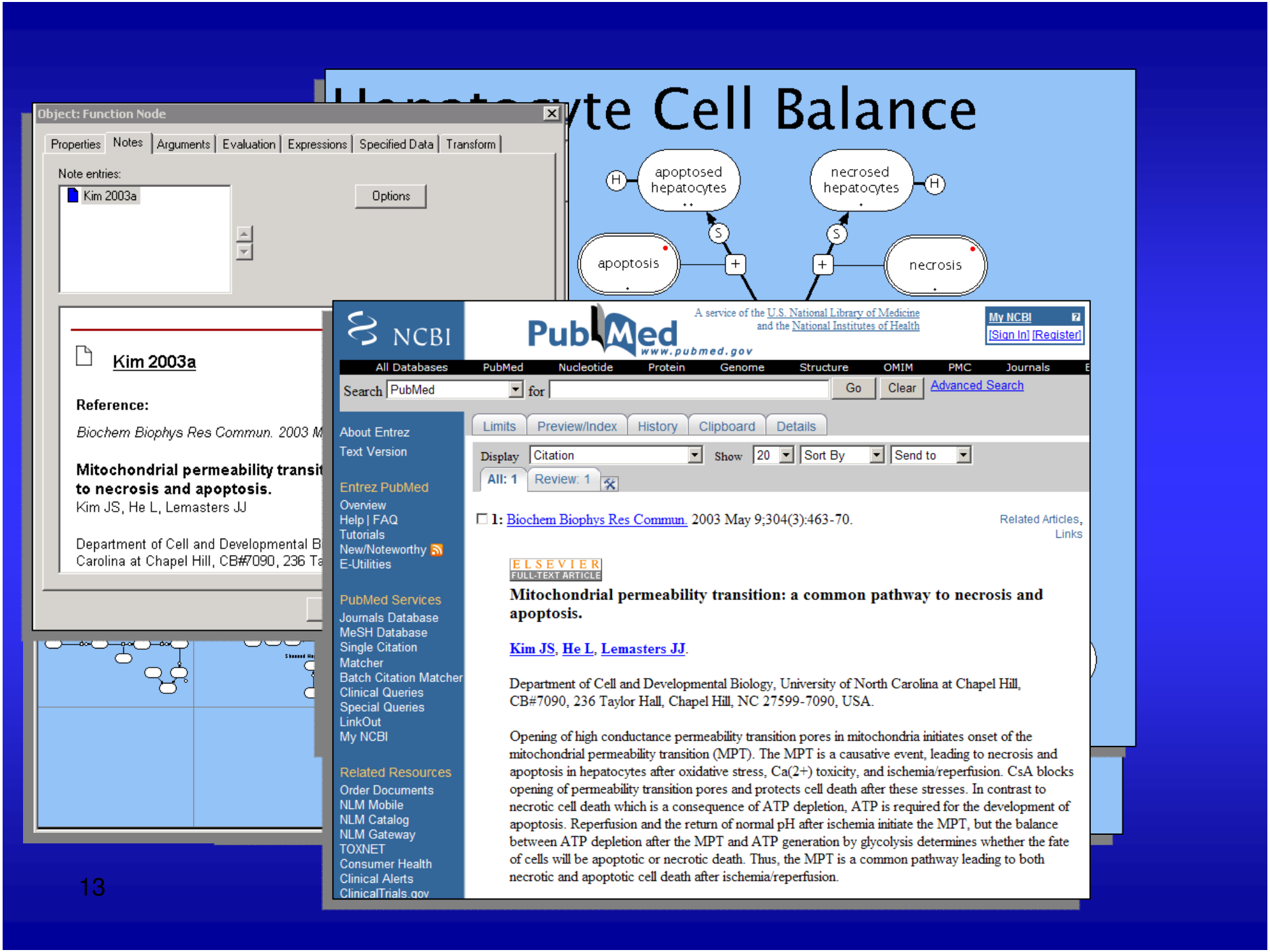
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Mitochondrial permeability transit
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1: Biochem Biophys Res Commun. 2003 May 9;304(3):463-70.
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ELSEVIER FULL-TEXT ARTICLE
Mitochondrial permeability transition: a common pathway to necrosis and apoptosis.
Kim JS, He L, Lemasters JJ.
Department of Cell and Developmental Biology, University of North Carolina at Chapel Hill, CB#7090, 236 Taylor Hall, Chapel Hill, NC 27599-7090, USA.
Opening of high conductance permeability transition pores in mitochondria initiates onset of the mitochondrial permeability transition (MPT). The MPT is a causative event, leading to necrosis and apoptosis in hepatocytes after oxidative stress, Ca(2+) toxicity, and ischemia/reperfusion. CsA blocks opening of permeability transition pores and protects cell death after these stresses. In contrast to necrotic cell death which is a consequence of ATP depletion, ATP is required for the development of apoptosis. Reperfusion and the return of normal pH after ischemia initiate the MPT, but the balance between ATP depletion after the MPT and ATP generation by glycolysis determines whether the fate of cells will be apoptotic or necrotic death. Thus, the MPT is a common pathway leading to both necrotic and apoptotic cell death after ischemia/reperfusion.

2 year goal

Provide a public knowledge platform for liver safety discussions during the drug approval process and post-marketing.

Hamner-UNC IDSS Team