Mechanisms of Drug Induced Liver Injury

Mechanism	Human Evidence	Key Assay / Principle for Initial Assessment
Mitochondrial Perturbation	50% of drugs w/ black-box warning for hepatotoxicity contained mitochondrial liability	**Glucose/galactose model (e.g. HepG2 glu/gal)**: molecules which disrupt mitochondrial oxidative phosphorylation increase cell dependence on glycolysis, reducing viability in galactose media
Bile Flow Perturbation	Arrest in bile flow leads to clinical cholestasis; progressive familial intrahepatic cholestasis type 2 (PFIC-2) caused by mutations in bile salt export pump (BSEP)	**Polarized functional hepatocytes (e.g. sandwich-cultured or HepaRG)**: effects of molecules on biliary excretion and hepatic transporters can be measured if bile canaliculi are formed and transporters correctly expressed
Reactive Metabolites	Reactive metabolites are formed from numerous drugs known to cause hepatotoxicity	**Metabolite identification (e.g. met. ID in microsomes, hepatocytes)**: molecules which form reactive intermediates can form detectable and sometimes isolable metabolites (e.g. GSH-adducts, glucoronides)
Lysosomal Perturbation	Some drugs causing phospholipidosis associated with liver injury, but still debated whether accumulation of phospholipids in lysosomes is actual cause of injury	**Cellular imaging assays (e.g. LipidTOX)**: accumulation of phospholipids induced by molecules can be detected through imaging using with lipid stains
ER Stress	Elevated ER Stress markers observed in vitro following exposure to drugs associated with DILI	**Unfolded protein response assays (e.g. BAC-GFP HepG2 reporter assay)**s: compounds which induce stress in the ER induce adaptive stress response pathways including the unfolded protein response (UPR), detectable through biomarkers such as ATF4 and CHOP
Immune Reaction	Innate immune cell infiltration observed in liver transplants or biopsies of patients with DILI	**No validated assays:** the immune response component of drug-induced liver injury remains difficult to predict or model