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Chimeric Mice with Humanized Livers Can Predict Human Drug Metabolism

In vitro and in vivo testing in animals have not always predicted human drug metabolism. The present study investigated whether chimeric mice could provide a more predictive assessment of the clinical metabolism of clemizole, a drug in clinical development for hepatitis C virus (HCV) infection. The results demonstrated that pharmacokinetics performed in chimeric mice correctly identified the predominant human drug metabolite. The differences in the rodent and human pathways for clemizole metabolism were of importance because the predominant human metabolite had anti-HCV activity. In addition, studies in chimeric mice correctly predicted that a drug-drug interaction would occur when administered with a CYP3A4 inhibitor.

See article at *J Pharmacol Exp Ther* 2013, **344:**388–396.

Kv2.x Channels Regulate Insulin and Somatostatin Release from Pancreatic Islets

Voltage-gated potassium Kv2.1 and Kv2.2 channels are highly expressed in pancreatic islets. Pancreatic β-cells from Kv2.1$^{-/-}$ mice display greater glucose-stimulated insulin secretion. Likewise, pharmacologic inhibition of Kv2.x channels enhances glucose stimulated insulin secretion from isolated wild-type mice and human islets but not in islets from Kv2.1$^{-/-}$ mice. These results suggest that inhibition of Kv2.1 may promote improved glucose tolerance. However, when Kv2.x inhibitors were administered in vivo, improved glucose tolerance was not observed, possibly because of the inhibition of Kv2.2. Therefore, the development of selective Kv2.1 inhibitors may provide new avenues to promote glucose-stimulated insulin secretion for the treatment of type 2 diabetes.

See article at *J Pharmacol Exp Ther* 2013, **344:**407–416.

Suramin Improves Regeneration of Ethanol-Induced Steatotic Partial Liver Grafts

Steatotic grafts are excluded for use in partial liver transplantation due to increased risk of primary nonfunction. This study investigated the effects of suramin on the outcome of partial liver transplants of steatotic livers taken from rats dosed acutely with ethanol. Serum alanine aminotransferase (ALT) and total bilirubin, and hepatic necrosis and apoptosis were significantly higher after transplantation of fatty partial grafts from alcohol-treated rats. Suramin decreased ALT by 60%, hyperbilirubinemia by 75%, necrosis by 83%, and apoptosis by 70% after transplantation. All fatty partial graft recipients died within 5 days without suramin treatment. In contrast, 62% of the rats receiving fatty partial grafts and suramin survived for 5 days because of inhibition of tumor necrosis factor-α and transforming growth factor-β formation.

See article at *J Pharmacol Exp Ther* 2013, **344:**417–425.

Insight to Explain the Cardiac Safety of Pixantrone in Doxorubicin-Treated Patients

Cardiotoxicity from the antitumor anthracycline, doxorubicin, correlates with cardiac drug levels, redox activation, and formation of the metabolite doxorubicinol. The cardiotoxicity may first be observed during salvage therapy with other drugs such as the anthracenedione mitoxantrone. In contrast, less cardiac toxicity has been observed in patients treated with doxorubicin followed by the anthracenedione pixantrone. In doxorubicin-pretreated human myocardial strips, pixantrone or mitoxantrone did not alter levels of residual doxorubicin. Mitoxantrone showed an unchanged uptake but synergized with doxorubicin for more redox formation. In contrast, pixantrone uptake was reduced, lacked redox synergism with doxorubicin, and inhibited formation of doxorubicinol.

See article at *J Pharmacol Exp Ther* 2013, **344:**467–478.