DIRECT AND CYTOKINE-MEDIATED EFFECTS OF ALBUMIN-FUSED HUMAN GROWTH HORMONE, TV-1106, ON CYP ENZYMES IN HUMAN HEPATOCYTES IN VITRO

Małgorzata Czerwińska, Paul Bolliger, Victor Piryatinsky, Hussein Hallak, Younss Sahly, Immaculate Amunom and David Buckley

XenoTech, LLC, 16825 W 116th St, Lenexa, KS, USA 2 Teva Pharmaceutical Industries, Ltd., 5 Basel St., Petach Tikva, Israel

Introduction
Drug-drug interactions involving therapeutic proteins that can modulate effects of cytokines and potentially influence drug metabolism have been of interest to regulatory agencies and pharmaceutical industry sponsors in recent years. The well-documented therapeutic protein ONAP agent involves prodrug metabolism, with a limited number of in vivo human studies have demonstrated the effect of individual cytokines on their metabolism and transporters (Evers et al., 2012).

Results
Figure 1 presents the experimental design of the study. This design is a subset of the US Patent 8445170.

Materials & Methods
Chemokine and receptors: TV-1106, mGHS and sterile drug vehicle were provided by Teva. LPS was purchased from Sigma-Aldrich (St. Louis, MO). Blood was donated by healthy volunteers who gave informed consent to participate in the study. Intravenous LPS and TV-1106 were purchased from EMD Biosciences (San Diego, CA).

Conclusions
We compared TV-1106, an albumin-fused GHS, and recombinant GHS to stimulate cytokine secretion in whole blood and the effects of the plasma of the released cytokines on hepatic drug metabolism in vitro. We found that GHS generally lead to human albumin alternative peptide cytokine response measured with a panel of proinflammatory cytokines in whole human blood. The cytokine stimulated by TV-1106 had little or no effects on CYP2C19 and CYP3A4 expression and enzyme activity in human hepatocytes.

References