Metabolomics-2013
OMICS Group Conferences
Accelerating Scientific Discovery
2nd International Conference and Exhibition on
Metabolomics & Systems Biology
April 8-10, 2013 Hilton Chicago/Northbrook, USA

Metabolomics and transcriptomics evaluation of preclinical biomarkers of hepatotoxicity: An update

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Abstract

Drug-induced hepatotoxicity represents a major reason that drugs are recalled post market. Furthermore, it has been estimated that 10% of acute liver failure is due to idiosyncratic events. While there is no standard definition for "idiosyncratic," the term is generally applied to compounds that induce a relatively low incidence of hepatotoxicity in humans and fail to exert liver damage using classical toxicity endpoints in commonly used preclinical testing species such as rats and dogs. The inability to identify such compounds with classical preclinical markers of hepatotoxicity has necessitated the need to discover new biomarkers that can ideally be translated into a clinical setting. In order to identify biomarkers of idiosyncratic toxicity, a systems biology study was initiated to evaluate omics endpoints in urine, blood and liver tissue from rats dosed with compounds that have been shown to be overt hepatotoxicants, idiosyncratic hepatotoxicants, and negative hepatotoxicants. The two overt hepatotoxicants were acetaminophen (APAP) and carbon tetrachloride (CCl4). Five additional compounds have been studied; two are generally classified as idiosyncratic in nature, felbatol (FEL) and dantrolene (DAN), while the other three are considered to not cause liver injury, meloxicam (MEX), metformin (MET) and penicillin (PEN). Since idiosyncratic and non-hepatotoxicant drugs do not cause overt hepatotoxicity, doses were used to induce some adverse effect (e.g., a decrease in body weight) to provide a phenotypic anchor. Each of these studies affected the rats in different ways and an update on the transcriptomics and metabolomics analyses from these studies will be provided.

Biography

Richard D. Beger received his Ph.D. in theoretical biophysics from Purdue University in 1991. He has been at the National Center for Toxicological Research (NCTR), US FDA, in Jefferson, AR for the last fourteen years and is currently the Director of the Biomarkers and Alternative Models Branch in the Division of Systems Biology. He is an author or co-author of over 100 publications including 6 book chapters. After arriving at the NCTR, he initiated research activities using NMR-based and MS-based metabolomics methods to identify non-invasive and tissue-based metabolic biomarkers of drug toxicity, drug efficacy, disease status, and individual susceptibility.