Bradley L Urquhart, J Clin Toxicol 2014, 4:4
http://dx.doi.org/10.4172/2161-0495.S1.012

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Summit on
Toxicology & Applied Pharmacology
October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore, USA

# Decreased nuclear receptor activity mediates down-regulation of drug metabolizing enzymes in chronic kidney disease through epigenetic modulation

**Bradley L Urquhart**
Western University, Canada

Chronic kidney disease (CKD) is associated with a decreased expression and activity of several cytochrome P450 enzymes. This may result in drug-associated toxicity in CKD patients taking drugs that are metabolized by affected isozymes. The objective of this study was to determine the mechanism of hepatic drug metabolizing enzyme down-regulation in CKD. Hepatic CYP3A1, CYP3A2 and CYP2C11 mRNA expression were determined in rats with surgically induced CKD. Chromatin Immunoprecipitation (ChIP) was performed to determine nuclear receptor and epigenetic mediated differences in the promoter region of these enzymes. Hepatic CYP3A and CYP2C11 mRNA expression was significantly decreased in CKD rats compared to controls ($P<0.05$). RNA polymerase II binding to the CYP3A and CYP2C11 promoter regions was decreased in CKD rats ($P<0.05$). ChIP also revealed a decreased PXR binding to the CYP3A2 promoter in CKD rats ($P<0.05$). HNF4α binding to the CYP3A and CYP2C11 promoter regions was also decreased compared to controls ($P<0.05$). The decrease in PXR and HNF4α binding was concurrent with diminished histone 4 acetylation in the CYP3A2 promoter locus for nuclear receptor activation. The uremic toxin indoxyl sulfate also mediates a decrease in CYP3A expression. A novel mechanism of drug metabolizing enzyme regulation in CKD was demonstrated. The results show that decreased CYP3A and CYP2C11 mRNA expression is secondary to decreased PXR and HNF4α binding as a result of histone modulation in CKD. These data may partially explain why patients with CKD have a higher incidence of adverse medication events than patients with normal kidney function.

## Biography

Bradley L Urquhart obtained his PhD in 2006 in Pharmacology and Toxicology at Western University in London, Ontario. He completed Post-doctoral training at Vanderbilt University and Western University in Clinical Pharmacology. In 2009, he began as an independent Investigator at Western University. His lab focuses on changes in drug disposition in the setting of kidney disease.

Brad.Urquhart@schulich.uwo.ca