Published in final edited form as:

Drug Metab Rev. 2013 February ; 45(1): 1–2. doi:10.3109/03602532.2013.754577.

Nuclear receptors in drug metabolism and beyond

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PREFACE

We are happy to present this nuclear receptor thematic issue of *Drug Metabolism Reviews*.

The drug responsive regulation of the expression and activity of enzymes or transporters has long been appreciated. This regulation can affect the degree of absorption or elimination of drugs, and potentially alter the therapeutic or toxicological response to a drug. The molecular mechanisms by which drugs regulate enzyme and transporter expression have been elusive up until the 1998 discovery and characterization of the xenobiotic nuclear receptor pregnane X receptor (PXR), which was independently cloned in the laboratories of Steve Kliewer then at the Glaxo Wellcome (Kliewer et al., 1998), and Ron Evans at the Salk Institute (Blumberg et al., 1998). The discovery of PXR benefited from earlier work published by Phil Guzelian at the University of Colorado who suggested “cellular factor” and “DNA element” that are responsible for drug responsive regulation of the human and rodent CYP3A genes (Quattrochi et al., 1995; Barwick et al., 1996). The cellular factor turned out to be PXR and the “DNA element” turned out to be PXR response element. The xenobiotic receptor identity for the constitutive androstane receptor (CAR), an orphan receptor cloned in David Moore’s lab in 1994 whose physiological function was then unknown (Baes et al., 1994), was subsequently revealed. Masa Negishi’s lab at the National Institute of Environmental Health Sciences (NIEHS) was the first to purify CAR from hepatocytes as a protein bound to the phenobarbital responsive element in the CYP2B gene promoter (Honkakoski et al., 1998).

As xenobiotic receptors, PXR and CAR were initially shown to regulate the expression of Phase I P450 enzymes. Subsequent studies from many laboratories, aided by combinations of molecular biology, mouse genetics, structural biology, and drug metabolism studies, have led to the conclusion that PXR and CAR can function as master regulators of the xenobiotic response by regulating both Phase I and Phase II enzymes as well as drug transporters.

Nuclear receptor-mediated xenobiotic regulation is made up of a complex regulatory network. The complexity is manifested in the observations that: 1) nuclear receptors beyond PXR and CAR, such as farnesoid X receptor (FXR), liver X receptor (LXR), retinoid-related orphan receptor (ROR), are also involved in the regulation; 2) each receptor is capable of regulating multiple xenobiotic targets; 3) there is extensive crosstalk between receptors; 4) and many xenobiotic receptors exhibit a distinctive, yet overlapping, spectrum of ligands. More recently, it has become clear that the nuclear receptor-mediated regulation of enzyme

and transporter can not only impact drug metabolism, but it can also influence many physiological and disease pathways by affecting the homeostasis of endogenous chemicals such as bile acids, bilirubin, steroid hormones, glucose, and lipids.

We want to thank all of the contributing authors who are experts in the forefront of this emerging and exciting research field. Special thanks go to Dr. Jack Hinson, Editor-in-Chief, and Russ Prough, Associate Editor of *Drug Metabolism Reviews*, who proposed this thematic issue to us shortly before the 17th North American ISSX Regional Meeting in 2011.

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