

Special Section on Drug Metabolism and Regulation—Editorial

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The expression of drug-metabolizing enzymes when responding to stimulus signals is tightly regulated by a variety of transcription factors, including the nuclear receptors pregnane X receptor (PXR) and constitutive androstane receptor (CAR). These receptors are xenobiotic sensors that respond to environmental stimuli. The quest to understand the molecular mechanisms by which PXR and CAR control the expression of drug-metabolizing enzymes, including cytochrome P450s (P450s), has been one of the driving forces that established the current foundation of knowledge on the regulation of drug metabolism and disposition. Numerous scientists have made significant contributions to this research area, including the recipient of the 2016 Bernard B. Brodie Award in Drug Metabolism and Disposition, Dr. Masahiko Negishi (Fig. 1). This special section on “Drug Metabolism and Regulation” honors Dr. Negishi’s accomplishments with five articles by his former mentor, trainees, and close collaborators.

Dr. Negishi obtained a bachelor’s degree in Pharmacy from Kyoto Pharmaceutical University in 1968. Then he entered the Graduate School of Osaka University and trained under Dr. Tsuneo Omura. He obtained a Ph.D. degree in Biochemistry at the Institute of Protein Research in 1972 under the supervision by Dr. Ryo Sato. He started his academic career as an Assistant Professor at Kansai Medical University in Osaka from 1972 to 1976. After completing postdoctoral training at the Medical School of New York University from 1976 to 1979 and at the National Institutes of Health in Bethesda from 1978 to 1983, he has been a Principal Investigator at the National Institute of Environmental Health Sciences (NIEHS) for 38 years. Currently he is an NIH Emeritus Investigator.

A distinguished scientist, Dr. Negishi has published in his career over 150 papers in the area of drug metabolism with many contributions highly impacting the field. By utilizing site-directed mutagenesis and recombinant protein expression, he demonstrated that a single amino acid residue could determine the substrate specificity of P450 enzymes (Lindberg & Negishi, 1989). This study stimulated the investigations on functional characterization of genetic polymorphisms in the P450 genes, providing a basis for predicting individual’s drug-metabolizing capabilities and consequences for drug efficacy and toxicity. He characterized CAR as a phenobarbital activated transcription factor and depicted the cellular signal mechanisms that dephosphorylate CAR at Thr38 to activate its functions (Mutoh et al., 2013). These findings answered the long-standing questions that have lingered since phenobarbital was first reported to induce hepatic drug-metabolizing enzymes, placing CAR at the center of drug metabolism and disposition studies. He further extended his study to the other nuclear receptors with the intention of developing a general concept for the biologic role of conserved phosphorylation (Negishi et al., 2020). Phosphorylation of a given nuclear receptor confers for a novel function over its non-phosphorylated counterpart and provides nuclear receptors with a communication tool to integrate their activities with other signaling pathways. In addition, he also discovered phosphorylation of PXR within the conserved ligand-binding domain in both mouse and human (Hu et al., 2020). Further studies with the androgen receptor for phosphorylation of its conserved region demonstrated that the phosphorylated androgen receptor elicits an anti-prostate cancer signal. This implicates the phosphorylated form of androgen receptor as a novel drug target for cancer therapy (Yokobori et al., 2021). Moreover, Dr. Negishi’s group determined the first crystal structure from the phase II drug-metabolizing enzyme sulfotransferase family (SULTs), as well as multiple structures of enzymes involved in heparan sulfate (HS) biosynthesis that regulate a plethora of physiologic and pathophysiological functions (Pedersen et al., 2002). This work defined the catalytic mechanism for SULTs as well as HS biosynthesis and enhanced our knowledge of how environmental exposure can contribute to diseases at molecular levels (Shevtsov et al., 2003).

In this special section, Dr. Negishi’s graduate mentor, Dr. Tsuneo Omura, wrote a commentary on the perspective of the induction of liver microsomal P450s by chemical compounds (Omura, 2022). Dr. Omura provided a historical view of the research on P450 induction and particularly emphasized Dr. Negishi’s contribution to the establishment of molecular mechanisms in the induction of P450s by phenobarbital through activation of CAR. While his manuscript was undergoing peer review, Dr. Omura sadly died in January 2022. This commentary is his last scientific article, which will serve to memorialize Dr. Omura’s own seminal contributions to the field of P450 research, including studies on the regulation of P450s and, in particular, trafficking of P450s in the endoplasmic reticulum in addition to his pioneering discovery of the P450 spectral properties that marked the beginning of the P450 field.

During his tenure of 38 years at the NIH, Dr. Negishi trained over 100 postdoctoral and predoctoral fellows and undergraduate students. Some of his trainees have developed successful careers in academia as professors or principal investigators, leading their respective fields of research both nationally and internationally. Several of his trainees and collaborators have contributed articles to this special section.

ABBREVIATIONS: CAR, constitutive androstane receptor; NIH, National Institutes of Health; P450, cytochrome P450s; PXR, pregnane X receptor.



Fig. 1. Dr. Masahiko Negishi was the recipient of the Bernard B. Brodie Award in Drug Metabolism and Disposition, awarded by the Division for Drug Metabolism and Disposition of the American Society for Pharmacology and Experimental Therapeutics, in 2016. Photos are reproduced with permission from Dr. Masahiko Negishi.

Discovery and characterization of CAR modulators are important for the generation of chemical tools to dissect the biologic functions of CAR. Identification of CAR modulators is also useful for toxicity studies and assessment of drug-drug interactions during drug discovery and development. Dr. Paavo Honkakoski wrote a review article focusing on the main methods used to search for CAR modulators and discussing their essential features (Honkakoski, 2022).

CAR has also been demonstrated to play important roles in regulating glucose and lipid metabolism as well as cell proliferation. Understanding the biologic function and clinical impact of CAR can promote the development of novel approaches for clinical applications. A review article led by Dr. Hongbing Wang captures the clinical relevance of CAR by highlighting its role in metabolic disorders and cancer development (Stern et al., 2022).

In addition to serving as xenobiotic sensors for enzyme induction, PXR and CAR also play distinct roles in the control of hepatocyte proliferation and liver cancer development. Dr. Kouichi Yoshinari and his colleague wrote a review article to describe the differences at the molecular level, which may help to evaluate the human safety of chemical compounds and develop novel drugs targeting liver cancers (Yoshinari & Shizu, 2022).

To honor Dr. Negishi's contributions to the sulfotransferase field, particularly with respect to mechanism, specificity, and roles in biology, Pedersen et al. reviewed the literature over the last 25 years to highlight Dr. Negishi's contributions and how they have impacted our understanding of the sulfotransferase field (Pedersen et al., 2022).

Collectively, the papers in this special section provide advanced information on molecular mechanisms in the regulation of drug metabolism by nuclear receptors CAR and PXR as well as insights to the development in the sulfotransferase field.

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