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Cytochrome P450 Enzymes: The Old Pandora's Box with an Ever-Growing Hope for Therapy Optimization and Drug Development—Editorial

In 1841, the notion of drug metabolism in the body was coined with the discovery of hippuric acid as a metabolite of benzoic acid in urine of human subjects (Ure, 1841). Since then, there has been an explosive growth in our knowledge of the chemical disposition of small molecules in the human body. However, it was not until the 1960s that cytochrome P450 enzymes were identified and then recognized as the main players in small-molecule metabolism. The exponential increase in knowledge was ushered in by a progressive realization of the significance of drug metabolism and its impact on both the desired pharmacological action and the adverse effects, in addition to an incremental improvement of the accuracy and sensitivity of analytical instrumentation. Indeed, the previous five decades have witnessed a journey that started with a handful of human enzymes identified by their potential catalytic activity on certain drugs and ended with the identification of 57 genes with characteristic structural signatures following the conclusion of the human genome project.

With these impressive strides, tremendous progress was made not only in terms of drug candidate optimization, drug-drug interaction prediction, drug-related problems resolution, and dosage regimen optimization but also in regulatory requirements soliciting data regarding the major metabolic pathways and enzymes involved. Indeed, a considerable investigative effort in drug discovery is dedicated to design the "ideal" molecule structure providing the best pharmacokinetic/pharmacodynamic profile based on the predicted interaction with metabolizing enzymes. Nevertheless, the growth of knowledge and applications in this field will not cease to continue any time soon. Up to this day, genomic variations affecting the activity of these enzymes, and consequently drug disposition, effects, and/or side-effects, are identified. Many of these enzyme isoforms remain as orphan enzymes whose potential substrates have yet to be identified.

In this issue of *Pharmacological Reviews*, F. Peter Guengerich provides an encyclopedic account of the role played by individual human cytochrome P450 enzymes in drug disposition (Guengerich, 2024). The author provides the readers with a panoramic view of the landscape of the field, spanning the length and breadth of knowledge along the history of this discipline and across the spectrum of investigative work. The review starts by setting up the reader to appreciate the complexity and significant impact of these major players, narrating the history of their discovery and the major health issues resulting from the lack of the appropriate knowledge of drug disposition by cytochrome P450 enzymes.

The author then proceeds by giving a detailed account of traditional and novel approaches of in vitro and in vivo assessment of the roles of different cytochrome P450 enzymes in drug metabolism, outlining the pros and cons of each approach. Indeed, the discussion is extended to involve minor hepatic members of this enzyme family as well as those cytochrome P450 enzymes that oxidize physiological substrates. This is followed by a thorough account of the progress made in identifying potential substrates. Whenever possible, the author provided a speculative view of the possible role of these orphan enzymes in drug metabolism within the context of the available data.

To put the comprehensive discussion into perspective, the review concludes by outlining a number of practical considerations for drug metabolism in drug discovery and development. Concepts discussed include approaches to predict bioavailability, assessment of the contribution of genetic polymorphisms, how species differences could lead to variations in the assessment of metabolite safety, and finally the utility of different testing modules for the stratification of potential drug-drug interactions. The author proclaims that the concepts discussed in the article are of value to students and entry-level industrial pharmacokinetics scientists, yet both the depth and breadth of the discussion, together with the critical evaluation of the available knowledge in every tackled aspect, argue for a much further advanced impact of this review. The article marks an important milestone, marking our present state of knowledge up to the midthird decade of the 21st century. The

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aforementioned coupled with a concise and succinct writing style make this piece of literature an invaluable resource for researchers, educators, and students regardless of their seniority.

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