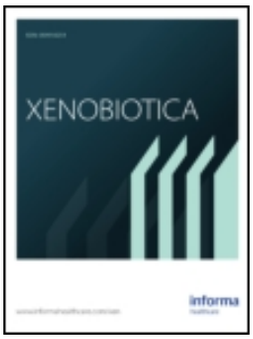

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Editorial

Editorial: The absorption, distribution, metabolism and excretion (ADME) transcriptome

The importance of drug metabolism in both drug therapy and safety is clearly established as a cornerstone of pharmacology, and progress of the former is crucially dependent on conceptual and technological advances made in a variety of scientific disciplines. The development of the science of drug metabolism has historically arisen from both the gradual acquisition of knowledge and quantum leaps derived from the recognition and understanding of multiple forms of drug metabolizing enzymes and transporters and their induction/inhibition, receptor-dependent regulation and pharmacogenetic variation in the human population.

The development of genomics, proteomics and metabolomics have all contributed substantially to drug metabolism research and increasing attention is now being placed on the transcriptomic analysis of the enzymes associated with the absorption, distribution, metabolism and excretion (ADME) of drugs. In general terms, the transcriptome may be considered as that subset of genes transcribed in given cell types and constitutes the dynamic link between the genome, the proteome, and the ultimate phenotypic expression in given cells and tissues. Accordingly, the ADME transcriptome encompasses those genes involved in the ADME of drugs and other xenobiotics, the regulation of which clearly provides a conceptually robust platform on which to understand drug action.

It is instructive to note that a PubMed search on 'transcriptomics' yields 227 hits and 'drug metabolism transcriptomics' yields 21, only a handful of which relate to toxicogenomics and metabolomics. Tellingly, 'ADME transcriptomics' or 'ADME transcriptome' both yield zero hits, indicating that these terms have not entered the mainstream lexicon of ADME research. Accordingly, it is the purpose of this special issue to consolidate emerging research on the ADME transcriptome focusing on the experimental tools used and the applications to ADME research in both drug development in the pharmaceutical industry and academic research, two closely interrelated spheres of activity.

The scene is set with two contributions from the University of Surrey (Nick Plant) and GeneGo, Inc. (Sean Ekins). Dr Plant poses the question of how one can logistically handle the information derived from the 800 genomes completely sequenced to date as it relates to ADME processes. The focus here is on phylogenetic, splice variant and SNP analyses of genomes and how one may predict both individual human responses to xenobiotics and the impact of population variance in response. Dr Ekins and colleagues address the network integration of the ADME transcriptome and describe commercially available algorithms (MetaCore and MetaDrug platforms) used for the assembly and analysis of human biological networks. Specific focus is placed on the networks associated with CYP3A4

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(a drug-metabolizing enzyme), PXR (a nuclear receptor that regulates several drug-metabolizing enzymes), hERG (an ion channel) and MDR1 (a drug transporter) as inputs.

Next follows a series of three articles from Rosetta Inpharmatics and Drug Metabolism, Merck Research Laboratories (Greg Slatter, Kelly Bleasby, Roger Ulrich and colleagues). The first deploys a 25K oligonucleotide microarray to assess the basal expression and xenobiotic-dependent regulation of the rat and mouse hepatic ADME transcriptome *in vivo* by 26 inducers. These authors provide a valuable compendium of rodent transcriptome expression data and further consolidate the concept of nuclear receptor cross-talk by illustrating the similarity between the resultant expression patterns elicited by PXR and CAR ligands. In addition, they clearly identify species-specific induction patterns across the rodent ADME transcriptome. The second contribution from this group addresses the human ADME transcriptome by profiling expression from 75 human liver samples. This study reveals that a plethora of the most highly variable human liver transcriptome genes are those involved with intermediary metabolism, inflammation, cell cycle control and most notably, drug metabolism. Another outcome of this study was to identify genes that have similar expression patterns to bellwether genes known to be regulated by the nuclear receptors AhR (CYP1A2), CAR (CYP2B6) and PXR (CYP3A4), providing valuable information on potential surrogate genes or protein markers of CYP induction.

The third contribution from this group addresses species differences, tissue selective expression in 22 tissues, and variability of expression in 75 human livers for more than 40 members of the ABC, SLC and SLCO transporter superfamilies that are known to play a role in drug transport.

Two clinical examples of the importance of understanding regulation and expression of the human ADME transcriptome then follow with contributions from St Jude Children's Research Hospital (Erin Schuetz and colleagues) and from Iconix Pharmaceuticals (May Lee and colleagues). The first contribution characterizes the human CAR transcriptome (ADME genes differentially expressed in phenobarbital-treated versus vehicle treated human hepatocytes) and the Hispanic liver ADME transcriptome (ADME genes differentially expressed in Hispanic versus Caucasian livers). This study concludes that there is a globally enhanced CAR ADME signature (CYP2B6 amongst other genes) in Hispanics with obvious implications for the careful consideration of drug dosage in the Hispanic population. The second contribution on drug–drug interactions concludes that of the 265 currently marketed drugs tested, 119 of them are CYP inducers and 83 are CYP suppressors. Put another way, of the 265 drugs examined, 76% of them influence CYP expression or function, underscoring the potential importance of drug–drug interactions. This latter contribution highlights the importance of the interpretation of large scale microarray gene expression data sets as not an end in itself, but rather an alert for potential clinical problems. Specifically, the clinical impact of these drug–drug interactions depends on the magnitude of the change but also that consideration should be given to the specific drug interaction. The latter is clearly exemplified by the fact that we would be concerned if there are interactions with drugs having a low therapeutic index such as warfarin and those having a high one, such as the penicillin-based antibiotics.

Two toxicological applications of the ADME transcriptome follow. First, a study from Gene Logic (Bill Mattes and colleagues) characterizes the transcription profile of enzymes of glutathione metabolism, a tripeptide intimately involved in both biological reactive intermediate inactivation and cellular homeostasis. Specifically, this contribution assesses the basal expression of glutathione-dependent enzymes in male and female rat, mouse and dog tissues and emphasizes their importance in safety assessment. Second, the contribution from AstraZeneca (Hugh Salter and colleagues) highlights the use of gene microarrays

in producing a hepatotoxicity profile that not only involves an ADME transcriptome fingerprint, but also forms the basis from which models of the mechanisms of hepatotoxic agents may be hypothesized and subsequently tested experimentally.

An interesting contribution from Syngenta (Fei Ling Lim) addresses the observation that approximately 2–10% of transcriptome genes are expressed in a circadian manner and that several xenobiotics can directly alter the expression of genes that control circadian rhythms. Finally, this special issue closes with a contribution from the NIEHS (Mas Negishi and colleagues) highlighting future areas of CAR and PXR research. Specifically, these authors highlight the fact that in addition to regulating the ADME transcriptome, these two nuclear receptors additionally cross-talk with endogenous stimuli resulting in regulation of physiological processes including energy metabolism and cell growth.

To conclude, we get the sense that an understanding of the ADME transcriptome is reasonably well established and that the technology is in place to define transcriptomic changes with both high specificity and sensitivity. We also discern that the future challenge is the cost-effective application of ADME transcriptomics and toxicogenomics to drug discovery, drug development and the safe clinical use of drugs. We hope that this special issue contributes to the debate in these areas and informs the future direction of basic and applied research in drug metabolism.

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