molecular pharmaceutics

editorial

Membrane Transporters in Drug Discovery and Development: A New Mechanistic ADME Era

Transporter biology is a rapidly emerging field of science that is an amalgamation of biological chemistry, pharmaceutical science, physiology, and pharmacology. Membrane transport proteins impact multiple facets of drug discovery and development. Translational pharmacology (the integration of drug disposition and drug action) is assimilating drug transporter knowledge into the clinical development plans of new therapeutics and known drugs. An integrated approach to transporter biology will reveal the influence of drug transport to better define and predict the pharmacokinetics, pharmacodynamics, and potential toxicity of xenobiotics and drugs. Of the 48 ATP-binding cassette (ABC) genes and approximately 300 solute carriers, a small percentage may directly contribute to drug action or toxicity, and we are only beginning to appreciate the magnitude of their effect on pharmacological and toxicological profiles. These interactions become even more complex if a transporter is the target of therapeutic modulation or if the transporter functions in a prodrug strategy.

The impact of transporter biology on many aspects of drug discovery and drug development is becoming increasingly recognized; however, there are many fundamental questions that remain unanswered. Will transporter characteristics of a new therapeutic become more important as we screen out clearance via drug metabolism? Is there a single transport process that contributes significantly to the pharmacology or disposition of candidate drug? What drug transporters are expressed endogenously in the cell lines that we use to determine drug−drug or drug−transporter interactions? What is the risk to successful drug development of ignoring or oversimplifying biological or chemical processes that we do yet not fully comprehend? To date, we only appreciate and fully understand a limited number of probe substrates or inhibitors, but can we exploit our limited knowledge of transporter biology to enable drug discovery and drug development? Does genetic diversity necessitate an understanding of transporter multiplicity? On the basis of our current understanding and bias, what are we missing? This and future issues of *Molecular Pharmaceutics* aim to embrace these challenges through an understanding of transporter multiplicity and QSAR, cross-species differences in transporter expression and function, and a better understanding of marketed drugs whose mechanistic disposition is different from what was originally believed.

Demonstrated originally to be a major determinant of the cellular multidrug resistance (MDR) phenotype, p-glycoprotein (ABCB1) is the best-understood drug transporter with significant progress being made in the 30 years since it was reported by Juliano and Ling.[1] Moreover, recognition that this transporter protects the brain from central nervous toxicity produced by ivermectin has provided significant proof of the role of this transporter in limiting the penetration of drugs into the brain.[2] In this issue of *Molecular Pharmaceutics*, P-Glycoprotein Recognition of Substrates and Circumvention through Rational Drug Design by Thomas Raub provides an excellent overview of our current state of knowledge with respect to the evaluation of structure−activity relationships in drug discovery. The greatest promise of transporter biology may relate to the prediction of drug disposition and action of future drug candidates, penultimately through *in silico* predictions. To this end, Patrizia Crivori and colleagues propose a computational model of P-gp. A commentary on membrane transport superfamilies (ABCs and SLCs) by Richard Kim provides preclinical and clinical examples of "when" and "why" transporter biology impacts drug discovery and development. However, Dr. Kim cautions that the "how" of transporter biology must be accomplished through systematic and careful interpretation of available methodologies. The Caco-2 cell line is one of the most utilized cellular models in preclinical development in predicting drug permeability. In the paper by Anna Calcagno and colleagues, ABC and SLC genes were compared among Caco-2 cells, normal colon, and colon cancer to determine whether the molecular fingerprint may serve as a model for colonic drug delivery or colon cancer.

The ability to move a test compound rapidly into the clinic and to plan effectively for its clinical development will in part depend on effective preclinical assessments of the interactions of drug candidates with drug transporters. Despite the potential significance of drug transport as a determinant of drug−drug interactions, very little has been standardized with respect to how best to determine the interaction of drugs with drug transporters preclinically and

(1) Juliano, R. L.; Ling, V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. *Biochim. Biophys. Acta* **1976**, *455*, 152−62.

(2) Schinkel, A. H.; Smit, J. J.; van Tellingen, O.; Beijnen, J. H.; Wagenaar, E.; van Deemter, L.; Mol, C. A.; van der Valk, M. A.; Robanus-Maandag, E. C.; te Riele, H. P.; et al. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. *Cell* **1994**, *77*, 491−502.

10.1021/mp058084b CCC: $33.50
Published on Web 02/06/2006

clinically. An article submitted by Shiew-Mei Huang of the Food and Drug Administration provides *in vitro* to *in vivo* strategies with respect to P-gp interaction. While many similarities may be drawn to the cytochrome P450 enzymes and metabolism-based drug−drug interactions, we should be cautious not to overgeneralize the complex and dynamic interaction of drugs, xenobiotics, and endobiotics with respect to transporter substrate selectivity and specificity. Moreover, the reality is that for many drugs (both old and new) the contribution of carrier-mediated transport at a molecular level to the most fundamental aspects of drug absorption, distribution, elimination, and drug action have only come to be fully appreciated in the past decade. Through the development of selective chemical inhibitors, model cell-based systems, and novel *in vitro* assays, we will be able to quantify individual transporter contributions. This combined with whole cell and organ assays will provide a context for rational hypothesis-driven science. A refined knowledge of drug transport function in genetically modified mice, nonclinical species, and the availability of exploratory Investigational New Drug paradigms will provide new mechanistic comprehension with respect to the integration of transporter biology (bench to bedside/bedside back to bench) in new drug discovery and drug development. We are entering a new and exciting era in drug discovery and development.

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