

## Transporter Role in Drug Efficacy and Organ Toxicity: Four Pillars of Clinical Trial Survival

Lai Y\*

Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Research and Development, Princeton, New Jersey, USA

\*Corresponding author: Lai Y, Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Research and Development, Princeton, New Jersey, USA, Tel: 609-252-6365; E-mail: Yurong.Lai@bms.com

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### Editorial

Lack of efficacy and safety issues leading to an insufficient therapeutic index are the most common reasons of drug candidate attrition by drug development phase [1,2]. In order to overcome inadequate clinical efficacy, a number of fundamental elements, also known as three pillars of phase II survival, were summarized [3]. These pillars include 1) sufficient drug concentration at the target site of action over a desired period of time is confirmed; 2) a drug binds the pharmacological target; and 3) the target expressed pharmacological activities desired. Moreover, in order to optimize safety profiles for sufficient therapeutic index, minimizing drug exposure to off-target sites/organs has been set as the forth pillar of clinical trial survival [4].

Membrane transporters consist of approximately 400 proteins that are categorized into two distinct superfamilies, the Solute Carrier (SLC) and ATP-Binding Cassette (ABC) families. The proteins transport nutrients such as amino acids, glucose and metabolic wastes across the membrane to sustain normal cellular and organ functions. Of those, only few membrane transporters (<10% of all membrane transporters) transport drugs and participate their absorption, disposition and/or excretion processes. As a result, transport of drugs across biological membranes has been intensely investigated to understand the impact of transporters on Pharmacokinetics (PK), Pharmacodynamics (PD) and safety of drug candidates. For example, drug transporters expressed on barriers of elimination organs such as the liver and kidney are functioned to facilitate the elimination of drugs from the body. Drugs that inhibit transporter activities or regulate gene expressions can significantly alter systemic PK and/or tissue exposure of other drugs that are substrates of those transporters, which are often the determinants of PD effect or organ toxicity. Optimizing drug Absorption, Distribution, Metabolism and Elimination (ADME) in general has been one important aspect of drug design. As such, drug hunters see increasing importance in understanding how membrane transporters affect drug absorption, disposition and elimination. In addition, given that many patients are on concurrent multi-drug therapy, altered transport kinetics due to inhibition, saturation or by change in transporter expression at disease state, can significantly alter blood concentration time profiles and/or tissue exposure of drugs. The study of drug transporter proteins has therefore become a critical early investment for reducing drug attritions during drug development phase.

The theory of that passive diffusion across biological membranes is the dominant route for solute transport and unbound plasma concentrations are in equilibrium across barriers has been challenged, followed by the discovery of membrane transporters that are found to play key roles in regulating drug organ exposure through uptake and/or efflux of substrate drugs. As a result, drug concentrations

measured in the plasma may not reflect the tissue-specific exposure [5]. Membrane transporters cause asymmetric tissue distribution for many molecules that are substrates of drug transporters. The transporter-mediated drug accumulation in organs is of particular interest in the pharmaceutical industry to attain a desirable therapeutic effect and safety profiles. Recently, the use of specific transporters has been shown to be a promising strategy for tissue-selective drug delivery to enhance the efficacy and/or reduce systemic toxicity [6]. On the other hand, active uptake of drugs may result in drug accumulation in an off-target organ to an unsafe level leading to organ-specific toxicity. The role of transporters on organ exposure supports the first and forth pillars of clinical trial survival. Thus, utilization of drug transporters for selective organ delivery to achieve favorable efficacy and safety profiles is a recent focus.

Drug transporters are key regulators of many fundamental physiological pathways. Inhibition of these critical pathways may lead to drug-induced organ toxicity [7,8]. Many endogenous molecules including nutrients, hormones or biosynthesis intermediates are transported by membrane transporters. Drug interactions with the transporters of physiologically important endogenous molecules such as serotonin, bile salts, bilirubin, carnitine, and thiamine may lead to drug induced toxicities. Since majority of the membrane proteins (>90%) are poorly characterized, studies on such interactions are warranted. Unexpected modulation of transporters by drugs may cause serious drug-induced toxicities that contribute to drug development attritions.

It remains very challenging to directly monitor transporter functions *in vivo*. Discovery of endogenous probes that could reflect the function of membrane transporters can greatly facilitate the understanding of transporter modulation *in vivo* [9]. The use of "omics" approaches, such as transcriptomics, proteomics or metabolomics becomes very popular tools to discover specific probes for monitoring transporter modulations or transporter related organ toxicity, despite very few endogenous probes for transporter function are available and data are controversial so far [10]. There is still a long way to go to elucidate the significance of membrane transporters in supporting pillars of clinical trial survival and the story will evolve as the data unfolds.

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