Pharmacogenomics in Drug Discovery and Development

Deepak Gupta*
LIE(C)OM Bradenton School of Pharmacy, Bradenton, FL, USA

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Use of pharmacogenomics principles have become a staple part during early drug discovery processes. Its application continues during preclinical and clinical drug development [3]. Absorption, Distribution, Metabolism, Elimination (ADME) chip like DMETTM Plus Solution Kits are now routinely used for profiling metabolic pathways [4]. These chips include some of the well-known variants in transporter genes, metabolizing enzymes like CYPs, safety/efficacy biomarkers and population specific biomarkers. This represents how drug discovery efforts based on pharmacogenomics are directly applied to pharmacology, translational as well as preclinical and clinical research [5].

Undesirable side effects and lack of efficacy are the two main issues leading to a drug’s failure in the clinic. Understanding pharmacogenetics associated with the drug has the potential to increase chances of its success in clinic. Personalized medicine in diseases like HIV, epilepsy, cancer, thrombosis has been steadily increasing as drug exposure in these disease states have been heavily influenced by polymorphism in enzymes, transporters and/or targets. Personalized therapy in oncology is a fast growing research area which is particularly influenced by inter-individual variability. Targeted therapies have already proved beneficial in certain patient population and drug discovery efforts have increased tremendously in the area of oncology [6].

To reap the full benefits of pharmacogenomics, genetic variability considerations should not only be included in early phases of drug discovery efforts (target and lead identification), but should also continue during preclinical and as well as throughout clinical trials. Although it may substantially increase the cost and time spent to understand genetic variability, it will serve as a powerful tool in the long run which will minimize drug failure rate in later phases of the drug development; where drug failure becomes a costly affair. Further, this can be useful to advance research efforts in areas of mapping, sequencing and decoding human genes. This can also be a helpful tool in developing animal models e.g. knockout mice to mimic genetic disorders. In addition to these benefits, advanced research efforts will help in evolving computation tools to help reduce cost of genetic testing, which has become a requirement for prescribing a few drugs. One of the well-known examples is the monoclonal antibody trastuzumab (Herceptin®) which can only be useful in selective population demonstrating HER2-positive breast cancer [7].

*Corresponding author: Deepak Gupta, Assistant Professor of Pharmaceutical Sciences, Director-Center for Drug Delivery and Targeting (CDDT), LIE(C)OM Bradenton School of Pharmacy, 5000 Lakewood Ranch Blvd, Office#233, Bradenton, FL 34211, USA, Tel: 941-782-5961; Fax: 941-782-5724; E-mail: dgupta@lecom.edu

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in all steps of drug development. It starts with assessing variability during target selection process followed by studying protein variants for metabolism and transport during preclinical studies. Phase 1 and 2 trials involve pharmacogenomics principles to include/exclude patients, optimize dose, understand magnitude of variability and use stratification biomarkers. Phase 3 trials mainly focus on dose and dosage form selection, long term efficacy & safety and identifying responders versus non-responders. FDA approval and post marketing surveillance mainly focuses on risk management, revising labels/indications and pharmacovigilance to understand variability based on patient response. Thus, clinical outcomes can be predicted with much more accuracy while decreasing attrition rate for a New Chemical Entity (NCE) to make it to the market.

References