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Pharmacogenomics in Drug Discovery and Development

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Mapping, sequencing and further decoding of human genome sequence in the last decade have completely revolutionized the drug discovery and development efforts. Out of ~3000 disease genes identified by human genome project, it has been estimated that ~500 are disease genes with druggable domains [1]. Currently marketed drugs only target <50% of these genes. This leaves us with hundreds of well-established but still under-utilized drug targets. It has been estimated that a drug with well-established target has much higher chances (~17%) of reaching preclinical development than a drug with not so established drug target (~3%) [2]. So, target identification and selection based on human genome sequence ensures much higher chances of success for the approval of a drug.

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 DMET™ 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 have 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].

Use of genetic data during drug development phases can help in identify possible Pharmacokinetic (PK)/Pharmacodynamic (PD) variability and dose can be adjusted accordingly. In addition, genetic data can be useful in understanding clinical outcomes due to drug-drug, drug-food or drug-transporter interactions. This type of information serves as an important pointer for future studies to apply inclusion/exclusion criteria. Understanding diagnostic genomic tests and use of adequate biomarkers also helps to stratify patient population based on safety, efficacy and dose adjustments. Overall, this will translate into time and cost savings leading to better drugs with well-defined safety and response.

Genetic variability can also be useful in understanding ineffective or unsafe prescriptions. In US alone, >3 billion prescriptions are written annually and millions of people depend on prescription and over the counter drugs to sustain their health. It has been estimated that >3 million of those prescriptions are either incorrect or ineffective. A non-efficacious drug decreases chances of survival while increasing additional cost to the patient. Deaths due to adverse drug reactions (ADRs) rank 4th-6th leading cause of deaths in US [8]. The cost associated with ADRs is expected to be >177 billion annually. Pharmacogenomics has the potential to minimize ADRs and some of the ADRs previously considered unpreventable may now be preventable due to better understanding of genetic variability [9-12]. These post-marketing experiences support the idea that pharmacogenetics should be involved early on in the drug development process and these post-marketing lessons are very beneficial in predicting clinical outcomes to a much better extent.

FDA now recognizes the importance of variability in intrinsic or extrinsic factors that can affects a drug's safety or efficacy. Although submission of genomic data may not be a requirement for all the drugs, FDA strongly recommends and encourages drug companies to submit genomics data into Voluntary Exploratory Data Submission (VGDS) program [13]. The Genomics Group of FDA's Office of Clinical Pharmacology in actively involved in developing procedures and policies for incorporating genetic variability during drug discovery and development. Use of adequate biomarkers, enzyme/transporter/target variants, dose optimization and patient's inclusion/exclusion criteria based on genetic variability increases chances of drug approval while minimizing time to approval [13].

In a nut shell, pharmacogenetic variability plays an important role

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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.

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