

Introduction to Pharmacogenomics in New Drug Development

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Pharmacogenomics has recently become an integral part of the drug development process. The pharmacogenomics revolution comes at a time when pharmaceutical companies are faced with mounting pressures to lower the cost of drugs development (Table 1). More than

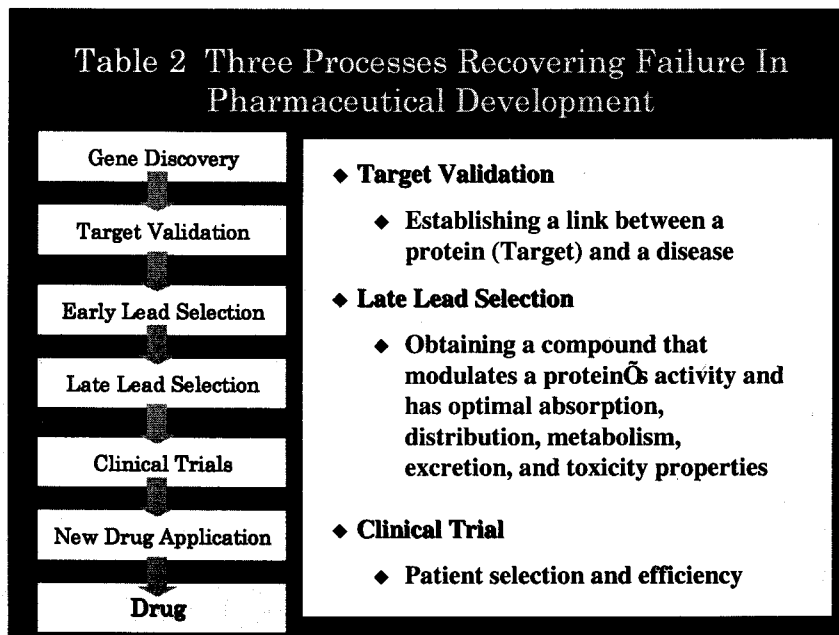
Table 1 Genomic Novel Drug Discovery Process

Genomic Research	Genome \oplus Transcriptome \oplus Proteome (mRNA) (protein)	
Gene Discovery	Positional Cloning Functional Cloning Expression Cloning	Bioinformatics
Functional/Structural Genomics	Espression Profile Comparative Genomics Transgenic & KO Animals	
Target Validation	Disease Model Pathology Pharmaco-proteomics	
Lead Hit & Optimization	Combi-Chem & HTS Rational Drug Design	
Pharmaco-Genomics Toxicogenomics	Pharmacogenetics Pharmacology Metabolism Bioavailability Pharmacokinetics	
Pre-Clinical Studies	Genomic Medicine Gene therapy Diagnosis	Tailor-made Medicine
Clinical Studies		

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twenty years of pharmacogenetic studies have established many of the genetic traits responsible for interindividual differences in the way patients metabolize drugs. The genetic polymorphisms found in the major drug metabolizing enzymes (DMEs) and their associated phenotypes are well established. These monogenetic traits have a predictable influence on the pharmacokinetic and pharmacological effects of a large number of

commonly prescribed drugs. This knowledge has been used to develop affordable, robust, clinical genotyping methods that can be used by pharmaceutical companies to screen patients prior to drug therapy (Table 2). Prospective screening of Phase I volunteers for



DME polymorphisms is done routinely at a number of pharmaceutical companies. As the pharmacogenomic initiatives at these companies evolve, more and more patients enrolled in Phase II-III clinical trials are genotyped to correlate efficacy with genetic markers that predict pharmacodynamic effects. There are a number of pharmacogenomic markers that provide useful diagnostic tools to prospectively evaluate treatment regimens, including the genetics of the host, cancerous tumors or infectious agents. The incorporation of pharmacogenomics into drug development offers the opportunity for pharmaceutical companies to evaluate drugs with a better understanding of the effect that specific genetic variants will have on drug response. Prospective testing can ensure the inclusion of important phenotypic subgroups, thus impacting the efficiency of drug development.

Pharmacogenomics is a rapidly evolving field that will certainly have an impact on drug

development. At present, pharmacogenomic testing is largely focused on drug metabolism genes and a map and SNP maps will provide an explosion of new drug targets, as well as variants that might be associated with patient response to therapy. It will be necessary for pharmacogenomic companies to validate that these markers are predictive of specific outcomes before they become useful in molecular diagnostics.

The speed at which this evolution takes place depends on several factors, including the development of platform technologies capable of delivering a cost effective analysis on a number of SNPs. In large part, the demand for pharmacogenomic testing as a component of drug development will depend on the mandates implemented by regulatory agencies.

Table 3 Goal and Strategy in Millennium Pharmaceutical Development

Goal

- Increase the productivity of current discovery & development process by over the 100% next four years
- Millennium will accomplish this using its comprehensive, integrated, and industrialized high throughput platform to revolutionize drug discovery & development

Strategy

- Select higher quality early-stage outputs to reduce late-stage failures
 - Decrease most costly and time-consuming type of failures
- Increase efficiency and throughput in bottleneck areas
 - Decrease cost
 - Decrease time

In summary, Pharmaceutical companies should be rethinking the old drug development paradigm and many investing in pharmacogenomics as a new approach to the discovery, development and marketing of new drugs (Table 3).