

Pharmacogenomics in Drug Discovery and Development

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Abstract

Pharmacogenomics is the study that examines how genetic variations affect the ways in which people respond to drugs. The ways people respond to drugs are complex traits that are influenced by many different genes. Pharmacogenomics intends to develop rational means of optimizing drug therapy, with respect to the patients' genotype, to maximize efficacy with minimal adverse drug reactions. Pharmacogenomics has the potential to revolutionize the practice of medicine, and promises to usher in an area of personalized medicine, in which drugs and drug combinations are optimized for each individual's unique genetic makeup. Indeed, pharmacogenomics is exploited as an essential step for target discovery and drug development in the pharmaceutical industry. The goal of the personalized medicine is to get the right dose of the right drug to the right patient at the right time. In this article, we will review the use of pharmacogenomics in drug discovery and development.

Keywords: targeted therapy, theragnostics

Introduction

Post-genomic biomarkers are now playing a critical role in making a prediction of transfer from preclinical to clinical development of drugs in terms of both safety and efficacy (Ozdemir *et al.*, 2007). This trend is revolutionizing diagnostics and drug development. For example, single nucleotide polymorphisms (SNPs) screenings will help target discovery and drug development since pharmaceutical and biotech companies can exclude patients whose drug screenings show that a drug being tested would yield adverse drug-related serious toxicities and ineffective efficacy to them.

Drug development currently takes too long and costs too much. The main reason that drug development is so

expensive is that it is so unproductive. DiMasi *et al.* (2003) estimated the average cost of bringing a new drug from the time of investment to marketing is \$802 million in year 2000 US dollars. Pharmaceutical Research and Manufacturers Association responded that the estimate of US\$ 802 million was likely to be conservative (Frank, 2003). At the 2006 Drug Discovery Technology conference, Steven Paul, executive vice president at Eli Lilly & Co., estimated that the cost of the new medical entity is currently \$1.2 billion, and warned that the cost of producing a successful drug could reach \$2 billion by 2010 unless the pharmaceutical industry can identify new and better ways to improve efficiency and effectiveness of drug discovery and clinical trials. Pharmaceutical companies can no longer afford to continue allocating the resources in cost-intensive later stages of clinical trials with drugs that are unlikely to have therapeutic effectiveness or are not better than the existing treatments. That is, the model for blockbuster drug development with large-scale markets is increasingly less viable. Pharmaceutical companies should be more careful in the selection of drug candidates at an earlier stage so that the only promising drug candidates get the full development resources (Kuhlmann, 2006).

Bringing a new drug to the market currently costs approximately \$1.2 billion, which makes it economically impossible to target small patient populations. However, targeting well-defined small patient populations will reduce the risk of failure and increase the likelihood of success of new drugs. Pharmacogenomics will allow us to identify genes with the highest likelihood of predicting efficacy for novel therapeutics and permit clinical trials to be substantially reduced in size. The ability to classify diseases into distinct molecular subcategories challenges traditional pharmaceutical business economic models of 'one-size-fits-all' drugs, i.e., blockbuster drugs, by aiding in identifying patients for whom the drugs will be both safe and effective. Pharmacogenomics could enhance the value of currently approved drugs with limited market share due to significant side effects or limited efficacy. Thus, the economic rationale for personalized medicine-driven healthcare decisions will be based increasingly on the cost savings realized through preventive interventions.

The blockbuster drugs that have been pursued by pharmaceutical companies carry high risks and high costs. New tools and technologies such as pharmacogenomics can be used to improve the quality of decisions in target discovery and drug developments (Jain, 2006). Pharmacogenomics

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promises to usher in an era of personalized medicine. The use of pharmacogenomics to identify biomarkers that have true predictive value would shorten development time and cost. Personalized medicine will help to achieve optimal medical outcomes by helping patients and clinicians select the disease management approaches that are likely to work best in the context of a patient's genetic and environmental profile.

The US Food and Drug Administration launched the Critical Path Initiative with the release of a report entitled "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" (<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>). The report indicated concern on the rising difficulty and unpredictability of drug development and called for a concerted effort to modernize the scientific tools and exploit the potential of bioinformatics for the evaluation and prediction of safety, effectiveness, and manufacturability of candidate drugs.

Projections on the future of pharmacogenomics are markedly different (Personalized Medicine Coalition, 2006). For example, projections range from pessimistic opinions (Williams-Jones *et al.*, 2003) to optimistic opinions (Ginsburg *et al.*, 2006). In this article, we investigate the use of pharmacogenomics in drug development.

Pharmacogenomics

Highly publicized adverse drug reactions and drug withdrawals have drawn serious responses from FDA. The number of FDA-requested alerts to potential adverse reactions, called as 'black box warning' or 'black label warning', has recently increased dramatically. Lazarou *et al.* (1998) reported more than 2 million serious adverse drug reactions a year in the United States, causing as many as 137,000 deaths. A personalized medical approach of a patient with disease will mean that the genetic profile of the patient will improve the diagnosis of the underlying cause of the disease and allow the selection of a specific drug treatment, which yields fewer serious adverse drug reactions (Phillips *et al.*, 2001). For example, Sconce *et al.* (2005) investigated the impact of genetic polymorphisms of two metabolizing enzymes, CYP2C9, and VKORC1, and recommended a new warfarin dosing regimens (Weinshilboum *et al.*, 2006). FDA advisory committee recommended genotyping for all patients receiving warfarin so that right warfarin dosing is given to the patient the first time to avoid adverse drug reactions (Womack, 2005).

The FDA approved a molecular assay called 'Invader UGT1A1' for use in identifying patients that may be at increased risk of adverse reactions to the drug Irinotecan HCl used in the treatment of colorectal cancer. UGT1A1

activity is reduced in individuals with polymorphisms of the UGT1A1*28 allele. In a prospective study of 66 patients treated with Irinotecan, patients with the 7/7 genotype (UGT1A1*28 homozygous) had a 9.3 times higher risk of grade 4 neutropenia toxicity than the patients with a 6/6 or 6/7 genotype (Innocenti *et al.*, 2004). The study of Innocenti *et al.* (2004) is the first prospective study with sufficient statistical power to show that patients with a UGT1A1*28 allele are at higher risk of grade 4 neutropenia.

Pharmacogenomics will help in aiding the right dose of the right drug to the right patients at the right time by predicting the probability of drug response based on the genetic makeup of patients (Mancinelli *et al.*, 2000). About 50% of all drugs are metabolized by the cytochrome P450 family of enzymes present in the liver and gastrointestinal tract. Differences in the sequence of a gene can lead the individual to a slow metabolizer or quicker metabolizer for certain drugs. Someone with too slow metabolism has an increased risk to be "overdosed" when given a typical dose, possibly resulting in serious toxicity. The typical dose may be ineffective for someone with quick metabolism, and thus a higher dose may be needed.

The FDA approved the AmpliChip, which is the world's first pharmacogenetic microarray-based test approved for clinical use. The AmpliChip CYP450 Test provides comprehensive coverage of genetic variations for the CYP2D6 and CYP2C19 genes. These genes account for the metabolism of an estimated 25% of all prescription drugs. The AmpliChip will help physicians make better decisions about drug treatments and dosages. Physicians can order AmpliChip test to find out if the patient has mutations in a gene that is active in metabolizing many types of drugs, including beta-blockers, antidepressants, antipsychotics, and some chemotherapy drugs.

Pharmacogenomics is used to target therapy to a subset of a disease. Genomic tests have enabled the identification of molecular targets specific to cancer cells, resulting in therapies that are likely to respond with enhanced therapeutic efficacy and less toxicity. Numerous cancer patients are benefiting from targeted drugs such as Erbitux (Cetuximab) for colorectal cancer patients with the presence of the biomarker EGFR, Herceptin (Trastuzumab) for breast cancer patients with overexpression of the biomarker HER2 protein, Retinoid (Vesanoid) for acute promyelocytic patients with the presence of the biomarker PML/RAR gene, Gleevec (Imatinib) for chronic myeloid leukemia patients with the presence of the biomarker Philadelphia chromosome positive.

Theragnostics

There has been minimal collaboration between pharma-

ceutical companies and diagnostic companies due to vast differences in expectations regarding price, clinical trial integration of diagnostic device and therapeutic drugs and time to market. The collaborations have been employed only in circumstances where adverse drug reactions threaten the viability of drugs or therapeutic efficacies are limited to a relatively small subpopulation. Recently, theragnostics, a term coined from therapeutics and diagnostics, receives increasing attention as pharmacogenomics moves to applications at point of patient care (Ozdemir *et al.*, 2006). Theragnostics is a combination of diagnostics and therapeutics that tailors treatments for individual patients based on their genetic profiles. Theragnostics will identify the subpopulation in which the therapy will be effective, and/or will yield serious adverse drug reactions through the detection of biological markers. This will drastically change the conduct of clinical trials, which will be performed in well-defined subpopulations of patients. Theragnostics will provide more effective care to patients and the possibility of avoiding ineffective treatments that might have serious side effects.

An example is the application of a new drug Herceptin (trastuzumab) for the treatment of patients with metastatic breast cancer. Herceptin is a monoclonal antibody directed at the human epidermal growth factor receptor 2 (HER2). Patients that overexpress HER2 in their tumors can be effectively treated using this antibody, while breast cancer patients who do not overexpress HER2 will not benefit from this medication. Herceptin is the first combination pharmacogenomics product.

Investigational New Drug (IND) application for Herceptin was filed in 1991, and phase III clinical trial was completed in March 1997. Phase III clinical trial showed

that Herceptin was not effective in treating patients with metastatic breast cancer, but a genetically based post-evaluation of the patients showed significant efficacy in women with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. HER2-positive metastatic breast cancer patients are estimated to comprise 25-30 percent of all breast cancer patients. These patients have a more aggressive disease, higher chance of recurrence, and poorer prognosis. Fast track designation was filed in March 1998 after compelling genetic association was presented to FDA. In September, 1998, FDA approval was made for combination of a diagnostic device and a therapeutic drug with HercepTest from Dako and Herceptin from Genentech/ Roche. HercepTest is the first FDA-approved diagnostic system which quickly and consistently identifies the most appropriate candidates for Herceptin therapy. In the absence of selection, the overall response rate of breast cancer patients is approximately 10%. However, overall response rate increases to 35-50% for patients selected on the basis of HER2 amplification. Therefore, HER2 selection is critical for the use of Herceptin in the treatment of breast cancer patients. Testing for gene amplification or overexpression of HER2 is now well established, required by FDA, and offers theragnostic value for treatment of women with breast cancer with Herceptin.

Another example is the application of a new drug Iressa (Gefitinib) for the treatment of lung cancer patients. Iressa was originally approved for the treatment of advanced non-small-cell lung cancer (NSCLC). Iressa was effective in reducing tumor size dramatically only in a small proportion of patients (Tamura *et al.*, 2005). Large phase III clinical trials did not demonstrate the improvement in

Table 1. Combination of therapeutic drugs and diagnostic devices

Drug Name	Test Name	Details
Herceptin (Trastuzumab)	HercepTest	Immunohistochemical test is designed to identify metastatic breast cancer patients with overexpression of HER2 protein. HercepTest is used to select breast cancer patients who may benefit from treatment with Herceptin.
Camptosar (Irinotecan)	UTG1A1	UTG1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. UTG1A1 is used to select colon cancer patients who may benefit from treatment with Camptosar.
Erbix (Cetuximab)	EGFR Pharma Dx kit	EGFR kit helps the detection of colorectal cancer patients who may benefit from the treatment with Erbix, which is a monoclonal antibody that targets a protein called the epidermal growth factor receptor (EGFR).
Gleevec (Imatinib)	c-kit	c-kit helps to detect the presence of the c-kit protein in gastrointestinal stromal tumor (GIST). C-kit helps in detecting patients who may benefit from treatment with Gleevec.
Tarceva (Erlotinib)	EGFR pharma Dx kit	EGFR kit helps the detection of non-small cell lung cancer patients who may benefit from the treatment with Tarceva, which is an EGFR inhibitor.
Purinethol (mercaptopurine)	TPMT	Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe PURINETHOL toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction.
Various drugs	AmpliChip CYP 450	AmpliChip test demonstrates if the patient has mutations in a gene that is active in metabolizing many types of drugs, including beta-blockers, antidepressants, antipsychotics, and some chemotherapy drugs.

survival for a general population of lung cancer patients. FDA's oncologic drugs advisory committee said that the confirmatory trial of AstraZeneca's Iressa showed a lack of overall survival benefit in the NSCLC setting. ViroLogic Inc. had an agreement with AstraZeneca to conduct a biomarker study with application to Iressa, a selective epidermal growth factor receptor kinase inhibitor. ViroLogic tested tumor samples from lung cancer patients treated with Iressa to evaluate the utility of these assays in targeting patients who would most likely get benefits from Iressa. Table 1 shows some of the products which use the combination of therapeutic drugs and diagnostic devices.

Targeted Therapy

Targeted therapy is 'a type of medication which blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with rapidly dividing cells'. The clinical development of traditional cytotoxic cancer agents is based on the assumption that the agents will reduce the size of tumors, and subsequently, the shrinkage of tumors will increase duration of the disease-free survival and overall survival of cancer patients. However, cytotoxic agents may lead to other organ damages, and may eventually lead to shorter overall survival of cancer patients since cytotoxic agents may kill normal cells in addition to cancer cells. In contrast, molecularly targeted agents are not designed to demonstrate tumor shrinkage but tumor growth inhibition. These agents may be more effective than cytotoxic agents since they will be less harmful to normal cells. Thus, these agents may provide clinical benefit such as longer survival and better quality of life.

Most molecularly targeted agents are less toxic than conventional cytotoxic agents. Thus, the maximum therapeutic effect may occur at doses well below the maximum tolerated dose (MTD). The intensity of dose-effect curve for toxic effect may not predict the therapeutic effect. Since dose-escalation is usually guided by toxicity in traditional phase I clinical trials for cytotoxic agents, such designs may be inappropriate for optimizing the use of molecularly targeted drugs (Ahn and Kang, in press). For example, Avastin (bevacizumab), a monoclonal antibody to vascular endothelial growth factor, was approved for the treatment of metastatic colorectal cancer by the U.S. Food and Drug Administration. The MTD of Avastin is 20 mg/kg due to the toxicity of severe migraine headache in some patients (Cobleigh *et al.*, 2003). In a randomized phase II trial of Avastin with chemotherapy, a 5 mg/kg dose yielded a higher response rate, longer median disease-free survival, and longer overall survival in patients with metastatic

colorectal carcinoma (Kabbinavar *et al.*, 2003).

The emergence of a growing number of molecularly targeted therapies challenges the traditional clinical trial paradigm in a variety of ways. There is an increasing need for novel statistical designs for clinical trials of molecularly targeted drugs since there is a growing need to determine a dose that yields optimal biological activity based on target inhibition or response rather than toxicity. The MTD of molecularly targeted drugs may be higher than the dose required achieving the maximum desired biological activity. Determination of the optimal biological dose (OBD) will provide more useful information for further drug development of molecularly targeted drugs. The first-generation target-based anticancer drugs such as Gleevec, Herceptin, and Iressa, are now regarded as established drugs.

Direction for Clinical Practice

Pharmacogenomics has the potential to revolutionize the way health care is provided. But, it is still in the stage of infancy. There are many challenging issues to be overcome to implement pharmacogenomics vision in clinical practice (Roden *et al.*, 2006). (1) Biological responses are complex since complex diseases are really complex. Disease and drug response can involve more than hundreds of genes. Environmental factors such as lifestyle, nutrition and age can influence disease and efficacy of the drug. (2) Rapid and reliable automated methods must be developed to efficiently conduct whole genome sequencing to examine the influence of genes to the susceptibility to disease and individual drug response. (3) Accessibility of genetic information and databases is an ethical and privacy issue since identified genetic susceptibility to disease may have implications for employers and insurance companies. (4) Cost for whole genome sequencing, SNP analysis and expression profiling are still expensive even though the cost is plummeting. (5) Health care providers or pharmacists have to receive education about new diagnostic tests, and use them to treat and advise patients. (6) Insurance companies may not want pay for extra diagnostic tests. (7) The development of complex systems for computer-assisted prescription will be required to actually use the genomic data. (8) Management of the data for individual patients will be essential for personalized medical care (Ratnain, 2007). (9) The value of pharmacogenomic study may not be known until the study is completed. (10) Financial constraints still plays an important role in the development of drugs with uncertain outcomes.

Pharmacogenomics has the potentials to be used for the entire drug discovery and development. Eventually,

pharmacogenomics test could be used at clinician's office as a way to get the right dose of the right drug to the right patient at the right time. Rapid access of reliable whole genome sequencing results is essential for the clinicians to provide personalized medical care, particularly in the prescription of drugs.

Pharmacogenomics receives increasing attention and is becoming an integral part of drug discovery and development although there are still many challenging issues to be overcome for the implementation of pharmacogenomics in clinical practice. Potential solutions are evolving rapidly. Genotyping costs are plummeting. It is possible that the era of a thousand dollar for whole genome sequencing will be coming in the near future. The cost of a thousand dollars seems a trivial cost considering that the whole-genome sequencing data are useful for the whole life. With the development of efficient data management system, management of the data for individual patients will be possible for personalized medical care. Pharmacogenomics is a young field that holds considerable promise for drug discovery and development.

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