Personalizing protein–drug interactions*

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Abstract: The development of new drugs today is a hugely expensive process, with estimated costs of up to $1 billion to take a drug through to market. However, despite this seemingly massive expenditure, statistics show that the great majority of prescription drugs on the market today are only effective for around 40 % of the patients to whom they are administered. Worse still, recently there have been a series of high-profile instances where potentially block-busting FDA-approved drugs have subsequently been withdrawn due to unanticipated side effects that were only revealed when the drug entered use in the general population. A variety of factors are at play in underpinning such statistics, but at the heart of the problem is the fact that, despite the extensive knowledge being generated in the postgenomic era about the genetic differences between individuals, Western medicine still today largely ignores such differences. The hope therefore is that by gaining a greater understanding of the individual nature of disease progression and of drug response, we might move toward a new era of personalized medicine in which the right drug is prescribed at the right dose to treat the precise disease afflicting the specific patient. As a step along this road, this review will discuss new approaches in the pharmacogenomics field to understanding in a quantitative manner the molecular consequence of polymorphic variation and mutation, both on encoded protein function and on protein–drug interactions.

Keywords: proteomics; protein-drug interactions; polymorphic variation; kinase; P450; p53.

INTRODUCTION

The pharmaceutical industry is today arguably facing an impending financial crisis due to an unsustainable increase in R&D spending with a concomitant decrease in productivity. Despite the rapid advances in fields such as genomics, proteomics, chemistry, and nanotechnology, which are fuelling drug discovery, the past decade has seen fewer drug approvals, escalating development costs and high-profile drug withdrawals [1,2]. Furthermore, despite these escalating costs, statistics show that the great majority of drugs on the market today are only effective for around 40 % of the patients to whom they are prescribed; in the anticancer field, this number is only around 20 % [5,12]. Worse still, recently there have been a series of high-profile instances where potentially block-busting FDA-approved drugs have subsequently been withdrawn due to unanticipated side effects that were only revealed when the drug entered use in the general population [2]. This suggests that current approaches to understanding key

questions of drug selectivity, efficacy, and safety before a compound enters clinical trials remain limited in their effectiveness and that new molecular approaches are therefore required. In addition, a lack of understanding of the variability in drug response between patients is thought to be a key part of the problem of the failure of drugs in development [3], so again, new approaches are needed here.

THE DRUG DEVELOPMENT PROCESS

The initial stage of development consists of the drug discovery period, in which libraries of compounds are initially synthesized and then tested in a variety of chemical assays and animal models. The second stage of the pipeline involves human clinical trials, which are divided into three phases: Phase I consists of a small number of healthy volunteers, and is mainly focused on ascertaining safe and tolerable doses of the drug, culminating in an initial estimate of the doses and regimens deemed likely to be most effective. In this phase, pharmacokinetic (PK) parameters such as adsorption, distribution, metabolism, and excretion (ADME) are first investigated, and any side effects are noted. During phase II, a larger group is recruited, consisting of individuals presenting the target disease or condition. In this phase, the most effective dose regimen is verified, and adverse reactions are monitored using increasing doses for longer periods. Phase III is similar, except it is randomized and controlled with hundreds and sometimes thousands of patients involved for final confirmation of drug efficacy and safety [4]. It is in phases I and II that pharmacodynamic (PD) parameters are of most concern: that is, the drug's effect on its targets (receptors and enzymes), downstream signalling events, and pharmacological response [5].

Costs of drug development

Each successful drug candidate now has to recoup between $0.5–2 billion [4], with an average cost of taking a drug through to market today estimated at around $800 million, most of which is absorbed by R&D costs of failed drug initiatives [2]. This figure is up from $54 million in 1976 and $231 million in 1987, representing an annual inflation rate of 7.4 % above general price inflation [6]. In addition to this cost escalation, 4 % of all approved drugs are later withdrawn (including Bextra, Vioxx, Baycol, Rezulin, and Tysabri), leading to lost income and potentially to expensive, high-profile litigation [2].

Even when a drug is successful, it is not necessarily profitable. A mere three out of ten approved compounds generate sufficient revenue to recover their average R&D costs [7,8]. To make matters worse, the development timeline has stretched to 10–15 years [2], while a typical patent length is 20 years [9]. This leaves drug manufacturers with less and less time within which to recover their costs before their patent expires and generic copies are permitted to enter the market [9].

Increasing attrition rates in the development process

A significant contributing factor to the escalation of R&D costs is the increasing attrition rate of new chemical entities (NCEs) [10]. Only 1/10 000 potential compounds survive the research pipeline from drug discovery through to approval [8]. According to the FDA, of those drugs entering phase I clinical trials, only 8 % are successfully registered compared with 14 % 10 years ago [11]. The attrition rate in phase II is now over 70 % and rising, and even in phase III almost one-third of molecules fail [10].

This high attrition rate indicates that the development process is not as effective as it should be in filtering out unsuitable drug candidates before they enter phases I–III clinical trials—and yet the clinical trials stage of the R&D process absorbs over 60 % of the total costs [8], a very significant proportion of which goes toward supporting phase III trials, the average size of which has nearly tripled in the past 20 years [3].

Drug efficacy and toxicity

In the past decade, the failure rate from unacceptable PK has been greatly reduced, due to improved preclinical screening of drug candidates [7,10]. Instead, the three leading causes of attrition in drug discovery are now attributed to problems with drug efficacy (30 %), safety and toxicology (33 %), and commercial reasons (20 %) [3,7].

However, even if a drug succeeds through each R&D stage and eventually receives approval, there is still no guarantee that the drug will deliver on its promises to the public. Current prescription drugs are typically effective in only 30–70 % of patients [5,12]. Worse still, with even some of the most advanced drugs a significant portion of the target population is likely to show adverse effects [5].

Many drug toxicities are only recognized at a late phase in clinical trials, after enormous resources have been invested in the drug candidate [2]. However, previously unobserved adverse drug reactions (ADRs) can also appear once a drug has been approved for use in the general population since, prior to approval, the drug has usually only been tested in ~1000–2000 individuals, groups that are only large enough to detect an ADR with an occurrence of 1 in every 250 people [9]. However, statistics from the United States show that >2 million cases of ADRs occur annually with 100 000 deaths [12], while drug-induced liver failure is the leading cause for acute liver failure [4]; this is clearly a major problem today and the costs associated with drug-related problems in the United States have more than doubled from 1995 to 2000—from $76.6 to $177.4 billion [13]. These statistics show that, despite massive expenditure on R&D, current drugs offer a very poor risk/benefit ratio for a diverse patient population.

This variability in drug response observed among patients is multifactorial: age, sex, body weight, diet, organ function, disease, co-medications, poor diagnosis, and genetic variation all play a role in determining the plasma concentration of a drug over time [5] and, therefore, its elicited pharmacologic effect on the drug's targets [12]. When the concentration is too low, the drug will be ineffective; when it is too high, it creates the potential for adverse effects.

One of these factors, genetic variation, has been shown to underlie many of these inter-individual differences in drug toxicity and efficacy [14]. Genetic variation can be observed in all of the principal effectors of ADME and drug response: drug transporters, drug receptors, drug-metabolizing enzymes, and drug targets, as well as the promoter elements regulating their expression.

PHARMACOGENOMICS, PHARMACOGENETICS, AND BIOMARKERS

In an effort to begin to get a handle on, amongst others, the variability in likely drug response, side effects, and toxicity in humans, the fields of pharmacogenetics and pharmacogenomics have been recently received increasing attention. The terms "pharmacogenomics" (PGx) and "pharmacogenetics" (PGt) are often used interchangeably [3,15]. PGt can be seen as a "subset" of PGx, and is defined as the study of the genetic variation resulting in differing drug response amongst individuals (usually only examining a few genes at a time). PGx looks at the entire genome, and the genetic variation seen at the cellular, tissue, individual, and population level, aiming to integrate our knowledge of pharmacology with modern advances in genome analysis.

The ideal of PGx is not only to understand the basis of the variation seen in drug efficacy and toxicity, but also to ultimately provide "personalized medicine" since the knowledge gained in this field has the potential to revolutionize the use of many medications [5,15]. Physicians will be able to prospectively identify patients at risk for severe toxicity or poor efficacy from a particular drug, by using genotyping kits to determine which alleles the patient has of genes important in its metabolism and response. PGx promises to provide a paradigm shift from "one-drug-fits-all" to "the right drug for the right patient at the right dose".

The many types of genetic variation in the human genome range from insertions, deletions, multiplications, or rearrangements affecting millions of base pairs to variations in single nucleotides. Of these, single-nucleotide polymorphisms (SNPs) hold the most promise for PGx analysis, as they are the

most common variant class [15]. Currently, there are >11 million known SNPs catalogued in the human SNP database, dbSNP [16]. SNPs can result in silent mutations, substitutions, the introduction of stop codons, or the alteration of mRNA splice sites—some of which can have a dramatic effect on protein function and hence on drug action [15]. However, even when the crystal structure of a protein is known, we still lack the ability today to accurately predict the effect of a mutation on the folding and function of that protein. For PGx to be effective, DNA markers, termed "biomarkers", need to be identified which correlate drug disposition and response to specific genes or polymorphisms. Biomarkers are defined as characteristics that are "objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention" [17].

The identification of biomarkers of efficacy and safety has been proposed as a fundamental change in development strategy needed to challenge increasing attrition rates [10]. These biomarkers should be used in early clinical development to prevent the progression of poor candidates to later stages—with the higher associated loss in investment when they fail. The use of PGx has been strongly encouraged by the FDA, and the development of biomarkers is a key component of the Strategic Research Agenda for the European Union's Innovative Medicines Initiative [10,18].

Effect of genetic variation on protein function and on protein–drug interactions

Fundamentally, PGx aims to draw correlations between genetic variation and drug response. However, >90 % of prescription drugs target proteins rather than DNA or RNA. Therefore, underpinning PGx effects is the manifestation at the protein level of polymorphic variation and/or mutation, both on protein–drug interactions, but also more fundamentally on protein function. Effects on protein–drug interactions can potentially be at a number of different levels, including modulation of the binding of the drug to its intended target, as well as alteration of the primary metabolism of the drug itself. Examples of each of these types of effect will be discussed below.

Variation in the genes encoding the tumor suppressor p53 and effect on protein function

Any cursory literature survey will show that p53 is one of the most cited proteins today, largely because of the role played by loss-of-function mutations in cancer. Many thousands of somatic and germ-line sequence mutations in p53 have been described, and mutations in p53 have been associated with greater than 50 % of all known cancers; as a result, p53 is now regarded as a viable therapeutic target. Perhaps surprisingly though, at the molecular level the effects of mutation on p53 function remain largely unknown, a fact which will obviously greatly hinder efforts to design drugs that might restore function to such "loss-of-function" variants. Recent work in the functional proteomics field has sought to begin to address this deficiency by using novel protein microarray technology as a miniaturized assay format to generate quantitative and genuinely comparative data on the effect of a set of 49 germ-line, cancer-associated mutations on the folding, DNA binding activity, and post-translational modification of p53 [19,20]. This study revealed that there are at least four different mechanisms at play in loss-of-function mutations of p53: (1) mutations that directly affect the DNA binding affinity of p53; (2) mutations that directly affect the integrity of the folded structure of p53; (3) mutations that affect both DNA binding affinity and the folded structure of p53; and (4) mutation that have no apparent effect on either DNA binding or folding p53 [19].

To date, few other such examples exist of such a quantitative, systematic study of the effect of polymorphic variation or mutation on the function of other proteins, yet it seems likely that as this type of chemical proteomic study is broadened to other proteins, knowledge of the diversity and subtlety of the effects of mutation on protein function will expand.

Human protein kinases as drug targets: A question of selectivity and of the effect of mutation on protein–drug interactions

With 518 members that are classified into phylogenetically distinct groups, protein kinases represent the largest enzyme gene superfamily in the human genome [21]. They play key roles in regulating a num-

ber of cellular processes including gene expression, mitosis, differentiation, and apoptosis, by coupling external stimuli to intracellular events through phosphorylation of specific subcellular substrates. Changes in the activity of protein kinases, as a consequence of over-expression and/or mutations, play a significant role in the development of various ailments such as cancer, diabetes, arthritis, and disease. As a result, kinases are now considered by many to be major drug targets for use in disease therapy [22]. Efforts toward the discovery of selective kinase-directed, small-molecule drugs (i.e., kinase inhibitors) have led to the synthesis of a number of these compounds able to disrupt aberrant activity which otherwise leads to a particular disease. Many of these compounds are in various stages of preclinical development, some already in clinical trials and a few, namely, Gleevec® (imatinib), Iressa® (gefitinib), Fasudil®, Herceptin®, and Avastin® have already been approved for treatment.

Almost all of the kinase inhibitors that are currently in development bind the ATP-binding pocket within the catalytic domains of the kinases and compete with ATP. In most cases, the ideal kinase inhibitor will block the activity of the intended kinase but no others. However, kinases have a very high degree of structural homology in their catalytic domains, so there is great potential for cross-reactivity, resulting in the inhibition of unintended targets. For example, published data on the selectivity of Gleevec, which was developed as a specific inhibitor of the chronic myelogenous leukaemia (CML) causative mutant Bcr-Abl kinase, indicates that this FDA-approved drug is not so specific and inhibits at least 15 other human protein kinases with submicromolar affinity [23]. So, while kinase inhibitors may hold great promise in treating disease, the conservation of the ATP-binding pocket clearly poses downstream challenges with target selectivity.

Recently, a number of groups have started to develop new approaches to specifically address the question of selectivity of inhibitors against panels of human protein kinases. Unlike solution-phase assays of individual purified kinases, the current generation of multiplexed, high-throughput kinase assays are typically based on competitive displacement of a labeled or immobilized inhibitor by the unlabeled drug. In one such in vitro approach, 119 human protein kinases (either full-length or the catalytic domains) were expressed recombinantly in *E. coli* and displayed on the surface of T7 bacteriophage in order to establish a phenotype–genotype link. A biotinylated, broad-specific kinase inhibitor, staurosporine, was immobilized onto streptavidin beads, allowed to compete with various test compounds for binding to the T7-displayed protein kinases and the amount of each phage bound to the staurosporine-beads quantified to determine the binding affinity of the test compound for each kinase [23]. Using this approach, the selectivity of 38 known kinase inhibitors was profiled against the kinase panel, allowing many novel, unanticipated interactions to be identified, including the potentially significant binding of Gleevec to the SRC-family kinase LCK (K_d = 63 nM) [23].

In another approach, protein function microarrays containing a set of 150 recombinant human protein kinases were used as a miniaturized, parallel assay format to determine the selectivity of the kinase inhibitors Iressa and staurosporine against the kinase panel. Here, the assay relied on the competitive displacement by the unlabeled inhibitors of fluorescently labeled, solution-phase ligands that each bind generically in the ATP binding pocket of a subset of the arrayed kinases. By carrying out assays on replica protein microarrays at varying concentrations of the unlabeled inhibitor but at a fixed concentration of the fluorescently labeled ligands, IC_{50} values could be determined for the unlabeled inhibitors for each kinase. By then determining the K_d value of each fluorescently labeled ligand for each kinase, the IC_{50} values could then be converted into absolute K_i values for the inhibition of each kinase by the unlabeled inhibitors. Using this protein microarray assay format, RIPK2 was identified as an unexpected potential off-target for Iressa (K_i = 31 nM) whilst staurosporine was found to bind to almost all the kinases in that panel, as expected [24].

Both of the approaches described above require access to extensive collections of recombinant human kinases, which might ultimately be limiting, particularly if any of the kinases require activation by phosphorylation, or if their drug-binding is modulated by protein–protein interactions that occur in vivo. A different approach to this problem, therefore, used mass spectroscopy-based iTraq™ technology to provide relative quantitation as well as identification of protein kinases bound to beads deriva-

tized with a panel of multiple broad-specificity kinase inhibitors ("kino-beads"). In these experiments, the kinases were native and derived from a crude mammalian cell extract; by repeating the assay in the presence of varying concentrations of an unlabeled solution-phase inhibitor, the IC_{50} values for the inhibitor binding to >250 native kinases could therefore be determined, providing a potentially powerful and rapid chemical proteomics approach to profiling kinase inhibitor selectivity against all kinases present in a cell or tissue type of interest [25]. Using this approach, several additional new potential targets of Gleevec were identified, including the receptor tyrosine kinase DDR1 (IC_{50} = 31 nM) and the oxido-reductase NQO2 (K_i = 39 nM) [25], suggesting amongst others that selectivity issues with kinase inhibitors that target the ATP binding pocket might extend beyond the kinase superfamily itself, at least into other nucleotide binding protein families.

While each of the approaches described above have their limitations, it seems that the path to improving our understanding of the molecular selectivity of drug candidates, both in the kinase field and elsewhere, may well now lie in further developments of such modern activity-based profiling approaches that improve coverage and sensitivity whilst allowing direct determination of K_i as well as IC_{50} values.

Notwithstanding questions of selectivity, the protein kinase field faces additional challenges with regard to the development of effective drugs. In particular, evidence is mounting that mutations to the protein kinase domain can have either positive or negative effects on the ability of a given drug to inhibit kinase activity. For example, Gleevec has been found to be highly effective in the treatment of early-stage CML, yet far less effective as the disease progresses, an affect that has been attributed to accumulation of mutations in the Ber-Abl kinase that destroy the binding site of Gleevec [26].

By contrast, the epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is over-expressed in the majority of non-small cell lung cancers. Such cancers seem to show a strongly elevated dependency, or even "addiction", to the EGFR activity; accordingly, a number of compounds are either already approved or in development as inhibitors of EGFR. One such compound is Astra Zeneca's FDA-approved anti-lung cancer drug, Iressa. However, clinical trial data revealed that Iressa is only effective on around 10 % of lung cancer patients and there seems to be some correlation between mutation in the tyrosine kinase domain of EGFR and susceptibility to the drug [27–29]. The molecular origins of this phenomenon are not currently well understood, nor is the correlation of mutational effects in EGFR with survival following treatment with Iressa. However, there are >130 clinically relevant SNPs/mutations known in this one protein domain alone [30], suggesting that much remains to be discovered at the molecular level about the effect of mutations on protein function and on protein–drug interactions in the case of EGFR and, by extension, in many other protein kinases.

Variation in the genes encoding cytochrome P450 enzymes and effect on drug response

The cytochrome P450s are a superfamily of integral membrane hemoproteins, named for their spectral peak at A_{450} when bound to carbon monoxide. The P450s metabolize a wide variety of compounds, including fatty acids, steroids, pesticides, flavourants and carcinogens [31,32]. However, they are best known for their role in the metabolism of pharmaceutical drugs and their involvement in ADRs and inter-individual variation in drug metabolism.

The majority of human P450s are bound to the endoplasmic reticulum membrane, and have a characteristic N-terminal hydrophobic signal-anchor sequence. They are mainly found in the liver, but are present in various other tissues such as the brain, prostate, skeletal muscle, and leukocytes. The main function of P450s in drug metabolism is the conversion of unreactive lipid-soluble substrates into more reactive and water-soluble products, by the insertion of an oxygen molecule derived from molecular oxygen. Two electrons are transferred sequentially during catalysis, with the NADPH-cytochrome P450 reductase enzyme acting as the donor of both electrons [31,32]. *Homo sapiens* has at least 57 functionally active cytochrome P450s, classified into 18 families [31]. Of these, the polymorphic CYP1, CYP2, and CYP3 families are responsible for over 40 % of P450-mediated drug metabolism [33]. The three main P450s responsible for the primary metabolism of the majority of pharmaceutical drugs are

CYP3A4, CYP2D6, and CYP2C9. These P450s are highly polymorphic, with over 99 different alleles reported for CYP3A4 alone [34]. This large degree of genetic variation in the P450s is one of the main factors leading to the variability with which patients respond to drugs [33]. Site-directed mutagenesis studies have shown that mutations can affect the substrate specificity, enantioselectivity, regioselectivity, and turnover rates of these enzymes.

Drug metabolism rates can differ over 1000-fold between polymorphic variants [33]. In some cases, the differing rates of drug metabolism observed are due to inter-individual differences in P450 expression level, however, the role of P450 genetic polymorphisms has emerged as the critical factor. These differences translate into variation in drug efficacy and the severity of adverse side effects.

P450s are implicated in ADRs when coadministered drugs compete for metabolism by the same P450, or when one drug affects the P450 activity necessary for the other drug's metabolism. Of all the drugs responsible for ADRs cited in studies, only 20 % of these are metabolized by nonpolymorphic enzymes—while 48 % of them are metabolized by the polymorphic P450s [33]. Polymorphic variation is, therefore, likely to account for a significant number of ADRs reported.

An area of ADR that is likely to increase, particularly in the developing world, relates to the ingestion of nonprescribed substances. Herbal medicines such as St. John's Wort, garlic, and ginseng have produced serious clinical interactions when coadministered with prescription drugs, although the herbal medicines are freely available over the counter and are widely perceived as "safe" [35]. An example that is particularly important in the African context is the widespread use of traditional medicines, such as African sweet potato, for treatment of HIV/AIDS, which when used in conjunction with pharmaceutical drugs such as efavirenz can lead to a potentially lethal ADR: inhibition of CYP3A4 by a component of African sweet potato blocks metabolism of efavirenz, which is itself otherwise toxic to human cells [36]. Current methods used in drug development seldom take the effects of P450 polymorphic variation into account, despite it likely being a major contributing factor to the high attrition rate of novel drugs in the costly development process [37]. Dosing of a novel drug is currently extrapolated from the ability of the general population to metabolize it, based on its average plasma concentration within the test population. This is obviously unsatisfactory, as just one study in Europe shows that approximately 13 % of the population are either ultra-rapid or poor metabolizers of drugs metabolized by CYP2D6. This implies that almost 40 million people are unable to benefit from the 20–30 % of drugs metabolized by CYP2D6 [33].

An often-cited example of the importance of PGx in drug metabolism is Warfarin, one of the most prescribed oral anticoagulants. Warfarin is used in the treatment and prophylaxis of thrombosis and embolisms, and is mainly metabolized by CYP2C9 [38,39]. The wild-type alleles are predominant; however, several polymorphic alleles are present which are associated with the risk of bleeding or over-coagulation at the standard dose. Depending on which variant alleles are present, these incidents can be life-threatening.

Another case in point is the metabolism of psychoactive drugs, including antidepressants, most of which are carried out by CYP2D6 [33]. The dosage required of these drugs corresponds closely with the patients' genotypes and can vary greatly: for nortriptyline, an antidepressant, it varies between 30 mg for poor metabolizers to 500 mg for ultra-rapid metabolizers.

It should be clear from the above discussion that there would be considerable potential benefit if it were possible to quickly, cheaply, and accurately assay drug candidates in a quantitative manner against not only wild-type cytochrome P450 enzymes but also against all clinically relevant polymorphic forms, both in terms of primary metabolism and also in terms of potential P450-mediated adverse drug interactions. However, few laboratories are readily able to engage in such studies today because typical high-throughput P450 assays rely on use of variable-quality microsomal preparations of P450s, together with access to banks of expensive automated liquid chromatography/mass spectroscopy (LC/MS) machines.

In principle, therefore, novel miniaturized assay formats might bring such analyses within the range of smaller companies and academic laboratories. However, miniaturizing P450 assays is not with-

out its challenges: for example, human cytochrome P450 catalysis requires the presence of at least one coenzyme, cytochrome P450 reductase, with which it does not form a stable complex and yet with which the correct orientation of the enzyme and coenzyme relative to each other is critical for electron transfer to occur efficiently. There have been a limited number of reports in which P450 enzymes have been immobilized onto glassy carbon or gold electrodes to functionally replace the cytochrome P450 reductase as the source of electrons [40]. It remains unclear though whether or not this biosensor-type approach will in general give rise to biologically meaningful data because the timing of the two electron transfers must be accurately coordinated with the reaction cycle. Other approaches to the miniaturization of P450 assays have, therefore, involved the encapsulation of microsomal P450 preparations in either agarose [41] or sol-gel droplets [42] prior to assay. However, while these approaches clearly work on a limited scale, there remains much scope for technological improvements in this area of chemical proteomics before the goal of P450 protein function microarrays can be considered to be properly realized: even if the P450 enzymes can be immobilized in a form that retains catalytic activity, existing P450 turn-over assays do not necessarily scale down readily, so it appears that, as with the kinase field, new, truly enabling activity-based profiling approaches are required here.

THE FUTURE: PERSONALIZING PROTEIN–DRUG INTERACTIONS

In recent publications, the FDA has espoused the broad view that drugs fail in clinical studies because we cannot today accurately predict how compounds will behave in people by extrapolation from laboratory and animal studies (see <www.fda.gov>) [11], and that new science is needed to guide the development process in the same way that it is accelerating the discovery process. They believe that the reason for the steadily decreasing number of new drug approvals each year is largely due to scientists testing new discoveries using outdated and inefficient tools and techniques, resulting in an inefficient and expensive drug development pipeline. In the FDA's Critical Path Opportunities List released in March 2006, modern scientific tools from fields such as genomics, proteomics, imaging, and bioinformatics are described, which provide the greatest opportunity for improving product safety and efficacy. PGx is highlighted as one such emerging tool, since the identification of biomarkers promises to give insights into disease stage, disease progression, drug response, and drug-dosing requirements [45]. According to FDA estimates, even a 10 % improvement in predicting a drug's failure before commencement of clinical trials could save $100 million in development costs for that drug—costs that would otherwise be passed on to consumers through higher insurance premiums and drug prices [1,3].

In March 2005, the FDA released the final version of its Guidance for Industry on the submission of PGx data [43]. The submission of PGx data is now required when valid biomarkers are available for drug efficacy and toxicity, where these biomarkers have already been rigorously tested by the scientific community and will clearly affect the design of clinical trials. When this is not the case, the agency encourages companies to voluntarily submit exploratory PGx data, and in turn promises not to use it when making regulatory decisions. The FDA hopes that this and earlier publications will help allay concerns in the pharmaceutical industry that the regulator might overreact to nonvalidated, exploratory genomic biomarkers and cause delays in drug development—which has led to the past reluctance of industry to introduce PGx and pharmacoproteomic studies into their drug development plans. The main challenge for the FDA is to encourage industry to submit voluntary data to speed up the arrival of the next wave of such products to the market [3,44].

It seems clear then that the future of both drug discovery and of drug administration will increasingly rely on data from PGx and pharmacoproteomic studies which can more accurately address issues of the molecular selectivity of protein–drug interactions, as well as questions surrounding the consequence of polymorphic variation or mutation on protein–drug interactions and on drug metabolism. With such information in hand, we might then begin to usher in a new era of personalized medicine in which the right drug is prescribed at the right dose to treat the precise disease afflicting the specific patient. Before this happens, though, there remains much work for chemical biologists to do in this space!

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