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Effect of Itraconazole on Pharmacokinetics of Paroxetine: The Role of Gut Transporters

Norio Yasui-Furukori, MD, PhD, Manabu Saito, MD,* Takenori Niioka, BS,† Yoshimasa Inoue,‡ Yasushi Sato, MD,* and Sunao Kaneko, MD, PhD**

Abstract: A recent in vitro study has shown that paroxetine is a substrate of P-glycoprotein. However, there was no in vivo information indicating the involvement of P-glycoprotein on the pharmacokinetics of paroxetine. The aim of this study was to examine the effects of itraconazole, a P-glycoprotein inhibitor, on the pharmacokinetics of paroxetine. Two 6 day courses of either 200 mg itraconazole daily or placebo with at least a 4 week washout period were conducted. Thirteen volunteers took a single oral 20 mg dose of paroxetine on day 6 of both courses. Plasma concentrations of paroxetine were monitored up to 48 hours after the dosing. Compared with placebo, itraconazole treatment significantly increased the peak plasma concentration (C_{max}) of paroxetine by 1.3 fold (6.7 ± 2.5 versus 9.0 ± 3.3 ng/mL, $P < 0.05$) and the area under the plasma concentration-time curve from zero to 48 hours [AUC (0–48)] of paroxetine by 1.5 fold (137 ± 73 versus 199 ± 91 ng*h/mL, $P < 0.01$). Although elimination half-life differed significantly (16.1 ± 3.4 versus 18.8 ± 5.9 hours, $P < 0.05$), the alteration was small (1.1 fold). The present study demonstrated that the bioavailability of paroxetine was increased by itraconazole, suggesting a possible involvement of P-glycoprotein in the pharmacokinetics of paroxetine.

Key Words: paroxetine, itraconazole, P-glycoprotein, interaction

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INTRODUCTION

Recently, it has become increasingly evident that drug transporters have a pivotal role in the pharmacokinetics of numerous drugs, with therapeutic implications.[1–6] Numerous studies have revealed that targeted expression of drug uptake and efflux transport to specific cell membrane domains allows for the efficient directional movement of many drugs in clinical use.[1–6] Transport by ATP-dependent efflux pumps such as P-glycoprotein influences the intestinal absorption[7,8] and renal[9,10] or hepatic elimination[11] and central nervous system concentrations[8] of many drugs.

Paroxetine is one of the selective serotonin transporter inhibitors and is widely used in the treatment of mental disorders, including depression, panic disorders, and obsessive-compulsive disorder.[12] Because paroxetine is metabolized by cytochrome isoenzyme P450 (CYP) 2D6[13] and inhibits CYP2D6 activity,[14,15] drug–drug interaction with paroxetine through CYP2D6 inhibition has been a significant concern. On the other hand, we showed a case in which digitalis intoxication was induced by coadministration of paroxetine through P-glycoprotein inhibition.[16] Also, a recent in vitro study demonstrated that P-glycoprotein inhibitory activity with paroxetine was more potent than the known P-glycoprotein inhibitor quinidine.[17] Another in vitro study reported that the cerebrum concentrations of paroxetine were higher in knockout mice.[18] Therefore, paroxetine is not only an inhibitor, but also a substrate of P-glycoprotein. To date, however, there are no in vivo data indicating that paroxetine as a substrate of P-glycoprotein is of clinical relevance.

The triazole antifungal agent, itraconazole, has a wide spectrum of antifungal activity in vitro.[19] Several studies have demonstrated a drug interaction between itraconazole and neuropsychiatric agents, including midazolam,[20] triazolam,[21] alprazolam,[22] haloperidol,[23] and bromperidol,[24] presumably as a result of inhibition of CYP3A4 by itraconazole. Meanwhile, P-glycoprotein reversal agents, including itraconazole, have been demonstrated to alter the pharmacokinetic properties of coadministered agents in therapeutic areas.[25,26] The effect of itraconazole was concentration-dependent with cimetidine's apparent permeability value for basolateral-to-apical transport decreasing from 3.96 to 1.92 × 10^{-6} cm/second ($P < 0.05$), resulting in a 50% decrease in efflux ratio. The MDR1-mediated transport of [3H]digoxin was inhibited by ketoconazole and itraconazole, and slightly by miconazole, suggesting that itraconazole has an inhibitory effect on P-glycoprotein.

Based on these findings, it is possible that itraconazole affects the pharmacokinetics of paroxetine. To our knowledge, there is no information about a drug interaction between itraconazole and paroxetine. The aim of this study was to confirm the effects of itraconazole, a transporting inhibitor, on the disposition of paroxetine.

METHODS

Subjects

Thirteen healthy Japanese volunteers (10 male, 3 female) were enrolled in this study. Their mean ± standard deviation

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From the *Department of Neuropsychiatry Hirosaki University School of Medicine, Hirosaki, Japan; †Department of Pharmacy, Hirosaki University Hospital, Hirosaki, Japan; and ‡MP-Technopharma Corporation, Fukuoka, Japan.

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Correspondence: Department of Neuropsychiatry, Hirosaki University, School of Medicine, Hirosaki 036-8562, Japan (e-mail: yasufuru@cc.hirosaki-u.ac.jp).

age (range) was 24.2 ± 3.5 years (range, 21–35 years) and mean body weight was 57.3 ± 7.2 kg (range, 45–67 kg). The Ethics Committee of Hirosaki University School of Medicine approved the study protocol, and written informed consent was obtained from each participant before any examinations.

Study Design

A randomized crossover study design was conducted at intervals of 4 weeks. Two 50 mg capsules of itraconazole twice daily (8 AM, 8 PM) or matched placebo with 240 mL of tap water were given for 6 days. The volunteers took a single oral 20 mg dose of paroxetine at 9 AM on day 6 with 240 mL of tap water. Compliance of test drug was confirmed by pill count. No other medications were taken during the study periods. No meal was allowed until 4 hours after dosing (1 PM). The use of alcohol, tea, coffee, and cola was forbidden during the test days.

Sample Collections

Blood samplings (10 mL each) for determination of paroxetine were taken into heparinized tubes just before and 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours after the administration of paroxetine. Plasma was separated immediately and kept at −30°C until analysis. At the time of blood samplings, blood pressure and heart rate were measured. Any adverse events were reported by subjects.

Assay

Plasma concentrations of paroxetine were measured using a high-performance liquid chromatographic method developed in our laboratory. In brief, the extraction procedure was as follows: to 2 mL of plasma sample was added 500 μL of 0.5 M NaOH, 100 μL of internal standard solution (200 μg/mL trifluperidol), and 100 μL of methanol. Thereafter, the tubes were vortex-mixed for 10 seconds and 5 mL of n-heptane–chloroform (70:30, v/v) was added as extraction solvent. After 10 minutes of shaking, the mixture was centrifuged at 2500*g* for 10 minutes at 4°C, and the organic phase was evaporated to dryness in vacuo at 40°C (TAITEC VC-960; Shimadzu, Kyoto, Japan). The residue was dissolved in 500 μL of mobile phase. A total of 400 μL was injected onto the HPLC system. The HPLC system consisted of Shimadzu LC-10AT high-pressure pumps, a Shimadzu CTO-10AVP column oven, a Shimadzu Work station CLASS-VP chromatography integrator (Kyoto, Japan), a Shimadzu SPD-10AVP (Kyoto, Japan), a Shimadzu SIL-10ADVP (500 μL injection volume) (Tokyo, Japan), and a column (STR-ODS II C18 150 × 4.6, 3 μm) (Shimadzu, Tokyo, Japan). The mobile phase was phosphate buffer (0.02 M, pH = 4.6), acetonitrile, and perchloric acid (60%) (57.25: 42.5: 0.25, v/v/v). The lower limit of detection was 0.5 ng/mL for paroxetine, and the values of the intraassay and interassay coefficients of variation were less than 5% at all the concentrations (2.5–150 ng/mL) of the calibration curve for paroxetine.

Date Analyses of Pharmacokinetics

The peak concentration (C_{max}) and the time to peak concentration (t_{max}) were obtained directly from the original data. The area under the plasma concentration-time curve [AUC (0–48)] was calculated using the lin-lin trapezoidal rule. AUC from zero to infinity [AUC(0–∞)] and elimination half-life were determined by noncompartment model with WinNonlin Professional software (Pharsight Co., Cary, NC).

Statistical Analysis

Data are shown as mean ± standard deviation in tables and mean ± standard error in figures. Paired *t* test was used for the comparison of the plasma drug concentrations between 2 phases, ie, placebo and itraconazole. The comparison of t_{max} was performed using the Wilcoxon signed-sample test. A *P* value of 0.05 or less was regarded as significant. Geometric mean ratios to corresponding values in the placebo phase with 95% confidence intervals were used for detection of significant difference. When the 95% confidence interval did not cross 1.0, the result was also regarded as significant. SPSS 13.0J for Windows SPSS Japan Inc., Tokyo, was used for these statistical analyses.

RESULTS

Appetite loss (n = 4, n = 7), abdominal disturbance (n = 4, n = 6), diarrhea (n = 1, n = 1), asthenia (n = 5, n = 6), and sleepiness (n = 3, n = 4) were observed in control and itraconazole phases, respectively. These side effects were mild to moderate and occurred 2 hours after doses of paroxetine and all recovered, at most, within 2 days after the doses.

Plasma drug concentration-time curves during both placebo and itraconazole treatments are shown in Figure 1, and their pharmacokinetic parameters are summarized in Table 1. There were 3 subjects whose plasma concentrations of paroxetine 48 hours after paroxetine dosing in the control phase were under the detection limit (0.5 ng/mL). We were not able to calculate the accurate average in all 13 subjects because of the 3 unavailable data. Therefore, we do not show

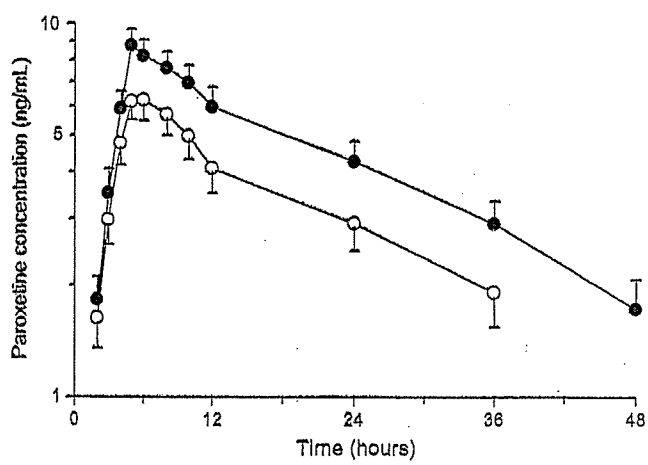

FIGURE 1. Mean plasma concentration-time curves of paroxetine after a single oral 20 mg dose of paroxetine. Open circles are control and solid circles are itraconazole treatment (100 mg twice daily for 6 days). Error bars indicates standard error. Control at 48 hours is not shown because of undetectable concentrations in 3 subjects.

TABLE 1. Effects of Itraconazole Treatment (200 mg for 6 days) on Paroxetine Pharmacokinetic Parameters After a Single Oral 20 mg Dose of Paroxetine in 13 Healthy Volunteers

Parameters	Control	Itraconazole	Ratio to Control
C_{max} (ng/mL)	6.7 ± 2.5	9.0 ± 3.3*	1.30 (1.01, 1.77)
t_{max} (h)	5.0 (4.0–8.0)	5.0 (5.0–8.0)	1.06 (0.92, 1.19)
AUC (0–48) (ng*h/mL)	137 ± 73	199 ± 91**	1.51 (1.08, 2.36)
AUC (0–∞) (ng*h/mL)	165 ± 93	256 ± 141**	1.56 (1.14, 2.39)
CI/F (L/hr)	159 ± 82	101 ± 48*	0.64 (0.53, 0.87)
Vd/F (L)	3479 ± 1576	2499 ± 1015*	0.73 (0.61, 0.98)
Elimination half-life (h)	16.1 ± 3.4	18.8 ± 5.9*	1.14 (1.01, 1.34)

*$P < 0.05$, **$P < 0.01$, comparted with control.
Data are shown as mean ± SD for pharmacokinetic parameters except for t_{max}.
Data for t_{max} are shown as median (range).
Ratio to control are shown as geometric mean (95% confidance interval).
C_{max}, peak concentration; t_{max}, time to peak concentration in plasma;
AUC (0–48), are under plasma concentration-time curve from 0 to 48 hours;
AUC (0–∞), AUC from 0 to infinity; CI/F, apparent total clearance; Vd/F, apparent volume of distribution.

the data at 48 hours in Figure 1. The percentage extrapolated AUC were 15 ± 7% for control and 21 ± 8% for itraconazole.

The paroxetine C_{max} during itraconazole treatment was higher than the corresponding value during placebo by 1.30-fold [95% confidence interval (95% CI), 1.01–1.77-fold]. The AUC (0–48) of paroxetine during itraconazole treatment was higher than placebo by 1.51-fold (1.08–2.36-fold). The total AUC of paroxetine during itraconazole treatment was higher than placebo by 1.56-fold (1.14–2.39-fold). Elimination $t_{1/2}$ of paroxetine during itraconazole was significantly longer than that during placebo [1.14-fold (1.01–1.34-fold)]. No change was found in t_{max} [1.06-fold (0.92–1.19-fold)].

There was no relationship between total AUC and the observed side effects after a single dose of paroxetine.

DISCUSSION

The results of this study showed a significant increase in plasma concentration of paroxetine (C_{max} and AUC) during itraconazole treatment. These findings imply that itraconazole increases the bioavailability of paroxetine or decreases the total clearance of paroxetine. Although itraconazole prolonged the elimination $t_{1/2}$ of paroxetine in this study, the alteration was small (14%). Therefore, it appears that the bioavailability of paroxetine was increased by itraconazole, which might be attributed to increased absorption of paroxetine in the small intestine or inhibition of extraction into bile in the liver.

Severely depressed patients tend to have dermatophytosis in skin, hair, and nails as a result of difficulties with self-care. On the other hand, systemic fungal infections remain a major clinical problem in immunocompromised patients and such patients tend to have negative thinking.[27] From a clinical point of view, it is more likely that itraconazole would be added to depressed patients treated with paroxetine. Thus, a pharmacokinetic interaction between paroxetine and itraconazole should be kept in mind by physicians, although the magnitude may not be large.

Several in vitro and in vivo studies have consistently suggested that paroxetine is both a substrate and an inhibitor of cytochrome isoenzyme P450 (CYP) 2D6.[13,14] Therefore, drug–drug interaction with paroxetine through only CYP2D6 inhibition has been a concern. On the other hand, the stimulation of the inhibition of the metabolic activities mediated by CYP1A2, CYP2D6, or CYP2E1 by 15 minute preincubation was not observed for any of the antifungal drugs, suggesting that these antifungal drugs, including itraconazole, are not mechanism-based inhibitors.[28] Furthermore, the ratio of risperidone/9-hydroxyrisperidone, an index of CYP2D6 activity, did not differ before itraconazole treatment (0.14 ± 0.13), after itraconazole treatment (0.15 ± 0.13), and 1 week after discontinuation (0.14 ± 0.13) ($P > 0.05$).[29] Therefore, it is unlikely that itraconazole inhibits paroxetine metabolism catalyzed by CYP2D6.

Because itraconazole is regarded as an inhibitor of CYP3A[20,21] as well as P-glycoprotein[25,26] based on several in vitro and in vivo investigations, it is possible that significant interaction between these drugs occurs as a result of inhibition of CYP3A. Consistently, drug interaction with itraconazole showed a large prolongation of elimination half-life of test drugs.[20–22] However, although statistically significant, alteration of elimination of half-life of paroxetine was small (14%). In addition, there were no data indicating the involvement of CYP3A4 in the metabolism of paroxetine but only CYP2D6. Thus, it seems that the drug interaction did not lead to an inhibitory effect of itraconazole on hepatic CYP3A.

An in vitro study reported that the cerebrum concentrations of paroxetine were higher in knockout mice, suggesting that paroxetine is a substrate of P-glycoprotein.[17] Meanwhile another study showed that neither verapamil nor P-glycoprotein-selective antagonist PGP-4008 affected the intracellular accumulation of [3H]paroxetine, [14C]phenytoin, [3H]clozapine, or [14C]carbamazepine in bovine retinal endothelial cells, indicating that these drugs are not substrates for P-glycoprotein.[30] We do not have a clear explanation for this discrepancy. Furthermore, in vitro studies are required to confirm the affinity of paroxetine as a substrate of P-glycoprotein.

There was no relationship between total AUC and the observed side effects after a single dose of paroxetine in this study. However, it is possible that itraconazole inhibits the activity of transporter(s) in the blood–brain barrier, resulting in higher paroxetine concentration in the brain. When both paroxetine and itraconazole are administered repeatedly for a long time, or if a more potent inhibitor of transporters than itraconazole is administered concomitantly with paroxetine, it would appear that careful monitoring of patients is required.

In conclusion, the present study showed that itraconazole increased paroxetine exposure, probably because of an increase in bioavailability through P-glycoprotein inhibition. Changes in the regulation of transporters such as P-glycoprotein may lead to a significant alteration of paroxetine pharmacokinetics.

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PERSPECTIVE

Mapping translational research in the age of theragnostics: from molecular markers to personalized drug therapy

Vural Ozdemir[1,2†], Bryn Williams-Jones[3], Dan M Cooper[1], Toshiyuki Someya[2] & Béatrice Godard[3]

†Author for correspondence
[1]General Clinical Research Center, School of Medicine, University of California, Irvine, CA, USA
Tel.: Tel.;
Fax: Fax;
E-mail: vural.ozdemir2@gmail.com
[2]Niigata University, Clinical Psychopharmacology Program, Department of Psychiatry, Graduate School of Medical and Dental Sciences, Niigata, Japan
[3]Université de Montréal, Groupe de recherche en bioéthique & Département de Médecine Sociale et Préventive, Montréal, Québec, Canada

Translational research is frequently used in the bioscience literature to refer to the translation of basic science into practical applications at the point of patient care. With the introduction of theragnostics, a new medical subspecialty that fuses therapeutics and diagnostic medicine with the goal of providing individualized pharmacotherapy, we suggest that the focus of translational research is shifting. We identify two bottlenecks or gaps in translational research for theragnostics: GAP1 translation from basic science to first-in-human proof-of-concept; and GAP2 translation from clinical proof-of-concept to development of evidence-based personalized treatment guidelines. GAP1 translational research in theragnostics is usually performed in traditional craft-based studies with small sample sizes and led by independent academic or industry researchers. In contrast, GAP2 translational investigations typically rely on large research consortiums and population-based biobanks that couple biomarker information with longitudinal 'real-life' observational data on a broad range of pharmacological phenotypes. Despite an abundance of research on the use of biobanks in disease gene discovery, there has been little conceptual work on whether and to what extent population biobanks can be utilized for translating genomics discoveries to practical treatment guidelines for theragnostic tests.

For biomedicine to improve human health, scientific discoveries must be 'translated' into applications at the point of patient care [101]. These applications can be information generating (for example, genetic tests that aid in prediction of disease risk or the individualization of drug therapy) or therapeutic (for example, new drug therapies and medical devices). Research that works between or at the interface of these two poles, that is molecular/preclinical investigations and practical applications in the clinic, is often referred to as 'translational research'.

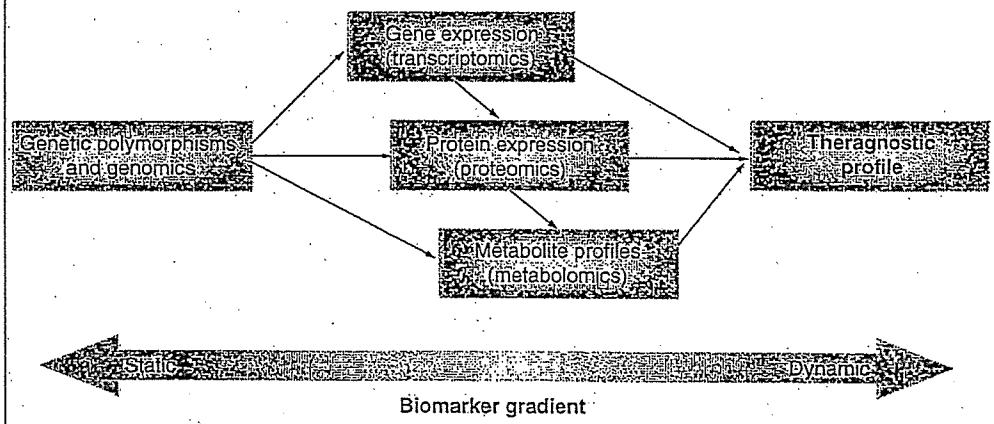
As an applied science, translational research has a prominent focus on clinically-relevant product development. In the present age of knowledge-based economies [1,2], translational research is increasingly visible and highly sought after by academics, research funding agencies and pharmaceutical or biotechnology industries. However, despite its frequent use in the scientific literature there has been little conceptual work that maps out the process of translational research. For example, is such research a multistage process with several qualitatively different subcomponents? And what does translational research contribute in the context of recent trends towards developing personalized drug therapies? Furthermore, we suggest that translational research is currently being reshaped by the introduction of theragnostics, a term denoting the fusion of therapeutics and diagnostics [3].

Theragnostics indicates a fundamental transformation in pharmaceutical research and medical therapeutics, that is, a move towards codevelopment, and by extension, coprescription of diagnostic tests and drugs to individualize treatment regimens. Unlike routine clinical chemistry (for example., plasma electrolyte measurements) or technology-driven biomarker approaches (for example., genomics), theragnostics does not focus on a single technology platform or marker set, such as blood biochemistry or genetic polymorphisms. Instead, theragnostics relies on an integration of technologies for gathering information from different levels of the biological hierarchy. Thus, a theragnostic approach might include not only pharmacogenomic tests [4] to identify the hereditary basis for individual or population variability in drug effects (whether based on genotype or gene expression), but also include proteomic [5] and metabolomic [6] tests to discern, respectively, the cellular proteins and metabolites formed and degraded under genetic or (patho)physiological influences (Figure 1). For example, trastuzumab (Herceptin®) is a monoclonal antibody directed at the human epidermal growth factor receptor 2 (*HER2*) for use in patients with breast cancer who are *HER2*-positive. Trastuzumab is widely claimed as one of the first generation of personalized medicines, because the drug is prescribed together with a theragnostic test to detect *HER2*

Keywords: biobanks, bioethics, biomarkers, General Clinical Research Center, theragnostics, personalized medicine, translational clinical research

future medicine

Figure 1. Hierarchy of biomarkers and their integration into theragnostic tests.



Hierarchy of biomarkers and their integration into theragnostic tests from gene sequence (upstream or static marker) to downstream (dynamic) markers on gene and protein expression or cellular metabolites. A theragnostic profile is depicted as a synthesis of various biomarker tests that characterize an individual patient and their drug treatment outcome. The theragnostic profile may be heuristic in nature when only a singular biomarker is associated with treatment outcomes while more mechanistic insights can be achieved when biomarkers from different levels of the biological hierarchy corroborate and complement each other (reproduced from [4] with permission).

overexpression; the test itself can use a variety of methods including gene (i.e., pharmacogenomic) and/or protein expression [7,8] Theragnostics is thus a more holistic approach (and not a singular technology) to diagnosis and therapy selection than has traditionally been the case in biomarker research or medical practice.

This paper identifies and differentiates two bottlenecks or gaps (hereafter referred to as GAP1 and GAP2) in the conduct of translational research in the emerging field of theragnostics. There is a major gap, GAP1, in the translation of basic science discoveries to first-in-human (FIH) proof-of-concept [9]. A second serious gap, GAP2, occurs in the transition from clinical proof-of-concept to the development of appropriate treatment guidelines and science policy. We suggest that resolution of these bottlenecks or gaps requires distinct research aims, resources and study designs. For example, research directed at GAP1 may require focused small sample size academic or industry-sponsored studies. In contrast, GAP2 translational research would require large-scale longitudinal population databases on observational 'real-life' treatment outcomes and core technical biomarker competency to explain variability in drug effects [10–12]. These gaps in translational research are collectively sufficiently important for the US FDA to have the view that, "the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process" [11].

'Unpacking' translational research in theragnostics

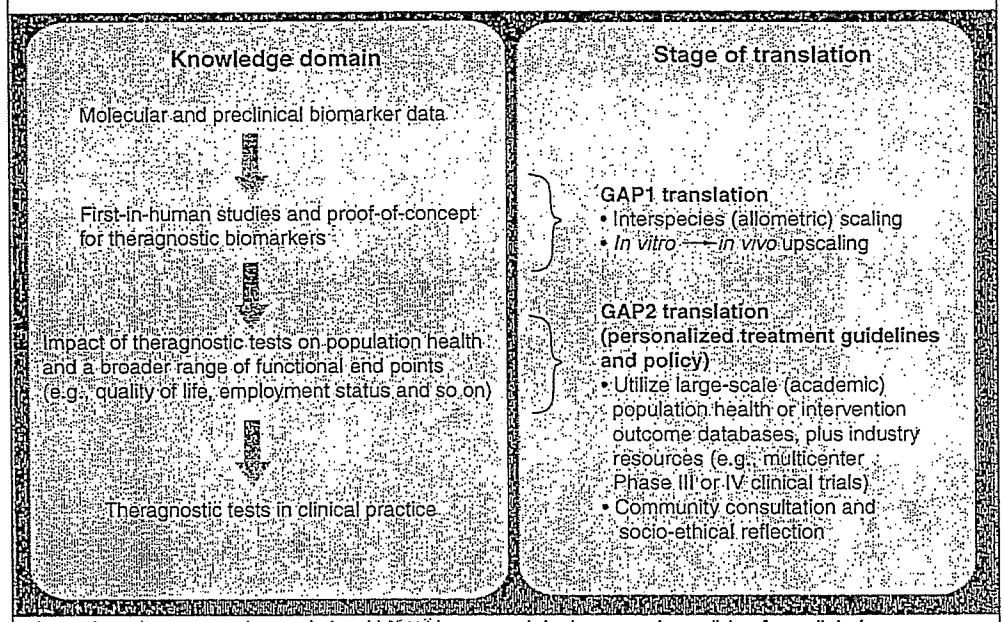
GAP1: translation from basic science to first-in-human proof-of-concept

The need for GAP1 translational research in theragnostics stems from three fundamental considerations:

- The obvious interspecies differences in pharmacokinetic pathways and molecular drug targets;
- The inevitable biological contrasts between the inbred laboratory animals with a homogenous genetic background and outbred human populations who exhibit marked genetic variability and exposure to a diverse array of social and environmental factors;
- The need for scaling up molecular observations *in vitro* to an integrated systems biology context in the whole (human) organism *in vivo* (Figure 2).

FIH proof-of-concept studies play a pivotal role in bridging the divide (i.e., GAP1) between preclinical biomarker research and large-scale population-based clinical investigations for theragnostic test development and validation. Despite their small sample size and limited scope

Figure 2. The projected two stages in translational biomarker research in theragnostic medicine.



The projected two stages in translational biomarker research in theragnostic medicine from clinical proof-of-concept (GAP1) to development of appropriate treatment guidelines based on theragnostic tests (GAP2).

of inquiry (usually less than 100 subjects per study), FIH studies make an important contribution as a first step in proof-of-concept and knowledge translation between *in vitro* and *in vivo* approaches, or more broadly, in extrapolation of data from animal models to the whole human organism. For example, clinical trials selectively testing patients with certain genetic subtypes of drug targets previously shown to confer an increased likelihood of response can facilitate proof-of-concept decisions on whether and to what extent a new molecular entity (NME) is a viable therapeutic candidate. An inadequate clinical response to an NME in such enriched samples may serve as an early indication of possible therapeutic failure in the general patient population [9].

A glance at leading clinical pharmacology and pharmacogenomic journals attests to the proliferation of genotype–phenotype correlative studies over the past 10 years [13,14]. Many of these studies fall under the GAP1 translational biomarker research; they often have small sample sizes. In an attempt to develop, implement, and disseminate a public genotype–phenotype resource, Stanford University (CA, USA), with funding from the NIH, established the Pharmacogenetics & Pharmacogenomics Knowledgebase (PharmGKB) [102]. This database is part of the NIH Pharmacogenetics Research Network (PGRN), a nationwide collaborative research consortium. The PharmGKB stores data regarding genetic sequence variation and their association with drug-related phenotypes, and provides methods for submission, browsing, and download. The PharmGKB is envisioned as an integrated research tool and repository for genetic, genomic, molecular and cellular phenotype data and clinical information on research participants in pharmacogenomics research studies. As of October 9, 2006, the PharmGKB reportedly contained information on 230 genes and its variants and 426 drugs. PharmGKB is comprised of clinical and basic pharmacokinetic and pharmacogenomic research data on, but not limited to, the cardiovascular, pulmonary and cancer pathways, and metabolic and transporter domains [102]. These data are publicly accessible on the internet for research purposes. In the short term, it is conceivable that biomarker data repositories such as PharmGKB will become an important aid to researchers in obtaining clinical proof-of-concept to understand how genetic variation among individuals contributes to differences in reactions to drugs. Looking further, such theragnostic databases may accumulate sufficient 'biomarker–phenotype' correlative studies to be able to inform population-based GAP2

translational research, a pivotal next step in developing theragnostic-guided treatments and health policy (see also section on GAP2).

It is noteworthy that studies aimed at GAP1 knowledge translation can be mistakenly framed as the sole translational research activity on the path from basic biomarker research to individually tailored drug therapy. Although the early phase translational biomarker studies noted above provide preliminary insights into predictive value (e.g., sensitivity/specificity) of theragnostic tests in humans, the complete range of pharmacokinetic and pharmacodynamic variability and attendant predictive performance of theragnostic biomarkers within and among human populations are seldom available at the end of GAP1 translational research. This becomes an acute concern, particularly in the case of theragnostic tests based on genomic, proteomic or other -omic technologies.

An important caveat in pharmacogenomic association studies aimed at personalized medicine is that they exploit the principle of linkage disequilibrium (LD), the co-occurrence of alleles at different genetic loci at a frequency greater or lesser than what would be expected due to random association alone [13,15,16]. Consequently, the genetic loci that are reportedly associated with drug response or toxicity may not necessarily correspond to the causal genetic variants. The degree of LD also varies markedly in different regions of the genome, as well as among different populations [17–19]. Thus, unless the causal genetic variants are ascertained, the informativeness of genetic markers identified in small-scale GAP1 translational research for prediction of drug response will be fraught with uncertainty when therapeutic forecasts are extended more broadly to other populations beyond the immediate study sample [20]. Furthermore, due to the multigenic nature of most human diseases and pharmacological traits, pharmacogenomic biomarkers can be, but are not always, population-specific; divergent sets of genes may influence the clinical phenotypes in different populations [20,21]. Attention to a large range of social and environmental factors (e.g., smoking, diet or other lifestyle factors) and gene–environment interactions will also be essential to appreciate individual, geographic and population variability in drug effects. Hence, these considerations collectively call for much larger scale population-based GAP2 translational theragnostic biomarker research.

GAP2: translation from clinical proof-of-concept to treatment guidelines based on theragnostic tests

For theragnostic tests and the personalized medicines to become a reality at point of patient care, a broader scope and types of human genetic (for example, other than single nucleotide polymorphisms), proteomic and metabolomic variation will need to be explained, well beyond what is achievable in small-scale GAP1 translational research studies. This is significant particularly from a clinical standpoint, as noted above, because the only barrier between a patient and severe toxicity or treatment failure will be the theragnostic test itself. In cases where the diagnostic sensitivity/specificity of the test is not sufficiently robust, a number of ethical and legal issues emerge related to knowledge transfer, regulation of novel technologies, commercialization and professional responsibility [7,22,23].

A case in point on the limits of GAP1 translational research is the CYP2D6 drug-metabolizing enzyme that contributes to disposition of several important psychotropic agents. Within the *CYP2D6* gene itself, certain alleles are typified by polymorphisms (for example, insertions/deletions) other than the traditionally investigated common nucleotide substitutions [24]. Attention to rare genetic variants will also be necessary in cases where the test results inform critical decisions on choice of drug prescription or dosage. The required sensitivity and specificity of molecular genetic assays, in a clinical diagnostic context, must be markedly higher than the technical standards acceptable for purely research purposes or biomarker discovery applications. Furthermore, clinicians who are familiar with the rapid turnaround times and relatively low cost of clinical chemistry tests may understandably demand a comparable ease of access, affordability and rapidity of test result (e.g., within several days or ideally by the end of each patient's visit). With the exception of a few specialized research centers and tertiary care centers in developed countries, these 'diagnostic standards' are simply not achievable or are well beyond the present capacity of public healthcare systems in many countries [8].

Another avenue for GAP2 translational theregnostics research, and one that has thus far been overlooked, is the use of population databases such as UK Biobank, the Estonian Genome Project, the Icelandic Healthcare Database and the proposed Quebec CARTaGENE project [10–12]. Thus far, the primary focus of these population databases has been the identification of

disease susceptibility genes with applications towards drug target discovery or disease risk assessment [25,26]. Conceivably, these biological and phenotypic/epidemiologic repositories can also contribute to the identification and/or validation of theragnostic tests to individualize drug treatment regimens. Potential benefits of population biobanks, and the means or research methodologies to achieve them over the long term, still remain ill-defined. The data contained in biobanks are quite variable in terms of content and quality, as well as the type of consent obtained from participating subjects. There is little harmonization or standardization of data collection and banking procedures amongst biobanks [103], making the exchange and sharing of data practically and financially difficult, a situation further compounded by common professional tendencies in biomedicine and human genetics research towards data withholding [10,27–29]. It would be timely to initiate key stakeholder meetings and wider community consultations to examine the impact of biobanks and theragnostic testing on medical practice, health professionals' education, awareness, professional responsibilities and how best to communicate and translate findings related to new theragnostic markers identified or validated in biobanks.

It is still unclear whether the dual objectives of biomarker validation for disease susceptibility and drug response variation are both achievable within the constraints of a single population biobank. For instance, disease phenotypes can be ascertained dichotomously as 'present' or absent'. In contrast, for drug response phenotypes to be clinically meaningful, they may require a higher resolution definition with continuous measures and repeated observations over time. Drug response may also fluctuate due to drug–drug interactions or time-dependent changes in physiological states (e.g., diurnal rhythms or menstrual cycle). Another more focused application of population biobanks could be the identification of gene–environment interactions in the context of drug therapy. Populations of patients who are tracked for their drug response over long periods of time can help to discover and validate rare but serious drug side effects during postmarketing safety assessments. Consider, for example, the relatively uncommon but lethal cardiac side effects of the selective cyclooxygenase 2 (COX-2) inhibitor rofecoxib (Vioxx®) that could not be detected reliably in small-scale early phase premarketing clinical trials. However, given the global nature of contemporary bioscience research, drug development, and marketing of new medicines, it is very likely that a coordinated multibiobank approach to theragnostic applications will be necessary.

Technical, bioinformatic and phenomic integration in theragnostics: rationale for centralized translational clinical research centers

Success in translational theragnostic research depends on expertise in three fundamental domains:

- Core technical expertise to generate high-throughput biomarker data;
- Collection of large volumes of phenotypic data from patients treated with drugs;
- Ability to perform correlative bioinformatics analyses between biomarker data and drug related phenotypes.

Due to the rapidly declining cost of genotyping and other biomarker genotypic technologies, availability of phenotypic data is now the most crucial and rate limiting step among these three domains [30]. This creates a statistical conundrum: in order to attain adequate statistical power to allow correction for multiple testing and association analyses among multiple biomarkers and clinical end points, researchers require an increasingly larger number of human subjects or biological specimens (for example, tumor biopsy material) to accompany the high-throughput theragnostic biomarker data [29,30]. Therefore, in addition to the technical integration, there is an acute need to establish local, national and international 'phenomic' databases that can integrate drug-related phenotypes across a broad range of treatment outcomes in different therapeutic areas, using both public and privately-sponsored pharmaceutical research and clinical trial data (a significant challenge given the proprietary, and thus secret, nature of such data).

To the extent that integration across technical (for example, amongst genomic–proteomic–metabolomic divides) and phenotypic dimensions is an emerging and timely theme in translational theragnostic research, what are some of the optimal research strategies that can deliver on this goal? We submit that one of the internationally recognized integrated models for translational clinical research is the General Clinical Research Centers (GCRCs), a national US network of approximately 78 centers, mostly located within the research hospitals of academic medical centers. The primary mission

of the GCRCs is to provide a research infrastructure for clinically oriented investigators. Furthermore, GCRCs act as an important link between molecular research and clinical practice, allowing investigators to translate knowledge gained through basic research into the development of new or improved diagnostics and therapeutics for patient care. With the emergence of theragnostics and increasing public demands for personalized medicine, it would be timely to amend the existing GCRC research infrastructure to accommodate integrated biomarker research towards the eventual goal of individually-tailored drug therapy. Conceivably, theragnostic-oriented GCRC networks can also serve to pool phenotypic information derived from industry-sponsored clinical trials (assuming stricter requirements for data disclosure) along with publicly funded academic pharmaceutical research across medical disciplines both at institutional, national and international levels.

Expert commentary & future outlook

Personalized drug therapy is not a new concept [15,16,31]. However, theragnostic testing is beginning to transform medical practice in a fundamental manner by placing a greater emphasis on the notion of probability [7,32], instead of traditional expectations about definitive prediction of treatment outcomes. The scope of research in this field has changed over the past several years with the availability of new technical and methodological approaches such as proteomics and metabolomics. At the moment, these promising technologies are best suited for exploratory research and remain to be validated both in terms of sensitivity/specificity of the data they generate and their mechanistic relevance in explaining variability in treatment outcomes in a population context. In parallel to these new technologies, the precision of existing technologies in applied genomics (i.e., high-throughput genotyping and gene-expression analysis) has increased while the unit cost of assays has markedly decreased.

Arguably, all these technical advances reflect an emerging 'engineering triumph' in biomarker research and more broadly, in diagnostic medicine [33]. However, for this to translate into a 'biological triumph' in a clinically meaningful manner, there is an acute need for the integration of biomarker data. However, our fear is that continued reliance on a singular biomarker technology platform by different stakeholders may result in an artificial compartmentalization (or fragmentation) of biomarker research. For example, human geneticists and pharmacogenomics researchers may favor genotyping and gene expression analyses, while biochemists may primarily utilize proteomic methods. On the other hand, drug effects are determined multifactorially, and the human genome is subject to poorly understood plasticity. Thus an integrated and promiscuous approach to biomarker technology platforms – whether they rely on genomic, proteomic and/or other methodologies – should be adopted so long as it explains individual differences in drug efficacy and safety in a mechanistic and clinically meaningful manner. It is against this need for technical and phenotypic integration that the new subspecialty of theragnostics and the attendant requirement for translational research centers are emerging.

Despite considerable efforts in GAP1 translational biomarker research, there remains a large and serious gap in further translation of biomarker data obtained in FIH pharmacogenomic proof-of-concept studies to a population level for the development of personalized treatment guidelines using genetic or other types of theragnostic tests. Large-scale biobanks are being developed in several countries around the world to meet these objectives. These databases concern the general population as opposed to particular patient groups or families. The amount of information gathered on the individual, as well as the types of diseases studied, constitute a divergence from the genetic registers of the past as well as from the gene-hunting (or discovery) research of today. Another change in the research paradigm is the desire for public consultation. These databases depend on public participation and assent. Therefore, it is important to encourage a free, open and useful dialogue among all stakeholders involved.

Due to the inherent focus on theragnostic 'product development', whether it be in biobanks or GAP1 translational research, there may be cause for concern over how much weight will be given to more fundamental research that may not directly have an application in the clinic [29]. Such concerns coincide with a shift in the perceived mission of academe and medical research, particularly with regards to the applied sciences. In addition to being sites of advanced teaching and research (the university's 'first' and 'second' missions), universities must now engage in knowledge transfer that leads to technology development and economic growth (the 'third mission'), a role that has proven popular with

governments, industries and universities worldwide [1,29]. To facilitate this third mission (and some would argue, to transform universities into 'entrepreneurial' institutions), laws and policies have been implemented to ensure strong protection of intellectual property rights and facilitate commercialization and technology transfer. Such patents can still have serious negative consequences for the conduct of academic research and free sharing of data amongst population biobanks [3,29].

Advances in theragnostics will likely take place in small but significant steps. Development of the necessary research resources – i.e., interdisciplinary research centers, harmonized large-scale biobanks, and so on – to enable the integration of molecular biomarker data with the attendant environmental factors, and the subsequent translation into clinical practice and regulatory frameworks needs to be planned much sooner. There is a clear need for translational clinical research centers that can integrate the full range of biomarker data from different levels of the biology and technology platforms (e.g., genomic, proteomic and metabolomic) as well as a broad range of pharmacological phenotypes (i.e., phenomics) in a way that is meaningful from both the physicians' and patients' individual perspectives.

Highlights

- In the context of theragnostics, translational research is clearly a complex and multistage process.
- Inadequate recognition of two major bottlenecks impedes the translation of current theragnostics research to the point of patient care: translation from basic science to first-in-human proof-of-concept; and translation from clinical proof-of-concept to development of evidence-based personalized treatment guidelines.
- The need to harmonize large-scale population biobanks to enable translation of theragnostics research is fraught with scientific, technical, social and political challenges. However, these challenges are not insurmountable.
- Broad public and stakeholder engagement is essential for the development of effective and socially acceptable biobanks that can allow a deeper understanding of both disease pathophysiology and individual determinants of variability in drug response and toxicity.
- The application of theragnostics at the point of patient care, i.e., the dream of personalized medicines, requires broad scale interdisciplinary collaboration along the development pathway, from rigorous basic and applied -omics research to the ethical implementation and delivery of safe and effective therapeutics.
- There is an acute need for resource development, for example, translational clinical research centers, for integration of biomarker data from different levels of the biology and technology platforms, as well as a broad range of pharmacological phenotypes in a way that is meaningful from both the physicians' and patients' individual perspectives.

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ORIGINAL INVESTIGATION

Asymmetry in Scientific Method and Limits to Cross-Disciplinary Dialogue: Toward a Shared Language and Science Policy in Pharmacogenomics and Human Disease Genetics

Vural Ozdemir, Bryn Williams-Jones, Janice E. Graham, Sheldon H. Preskorn, Dimitrios Gripeos, Stephen J. Glatt, Robert H. Friis, Christopher Reist, Sandor Szabo, James B. Lohr, and Toshiyuki Someya

Pharmacogenomics is a hybrid field of experimental science at the intersection of human disease genetics and clinical pharmacology sharing applications of the new genomic technologies. But this hybrid field is not yet stable or fully integrated, nor is science policy in pharmacogenomics fully equipped to resolve the challenges of this emerging hybrid field. The disciplines of human disease genetics and clinical pharmacology contain significant differences in their scientific practices. Whereas clinical pharmacology originates as an experimental science, human disease genetics is primarily observational in nature. The result is a significant asymmetry in scientific method that can differentially impact the degree to which gene-environment interactions are discerned and, by extension, the study sample size required in each discipline. Because the number of subjects enrolled in observational genetic studies of diseases is characteristically viewed as an important criterion of scientific validity and reliability, failure to recognize discipline-specific requirements for sample size may lead to inappropriate dismissal or silencing of meritorious, although smaller-scale, craft-based pharmacogenomic investigations using an experimental study design. Importantly, the recognition that pharmacogenomics is an experimental science creates an avenue for systematic policy response to the ethical imperative to prospectively pursue genetically customized therapies before regulatory approval of pharmaceuticals. To this end, we discuss the critical role of interdisciplinary engagement between medical sciences, policy, and social science. We emphasize the need for development of shared standards across scientific, methodologic, and socioethical epistemologic divides in the hybrid field of pharmacogenomics to best serve the interests of public health.

From the VA Long Beach Medical Center (V.O., D.G., C.R., S.S.), School of Medicine, University of California, Irvine, Long Beach, CA; Department of Psychiatry (V.O., T.S.), Clinical Pharmacology Program, Niigata University Graduate School of Medical and Dental Sciences, Niigata City, Niigata, Japan; Groupe de recherche en bioéthique et Département de médicine sociale et préventive (B.W.-J.), Université de Montréal, Montréal, QC; Department of Bioethics (J.E.G.), Faculty of Medicine, Dalhousie University, Halifax, NS; University of Kansas School of Medicine and the Clinical Research Institute (S.H.P.), Wichita, KS; Department of Psychiatry and Behavioral Sciences and Medical Genetics Research Center (S.J.G.), SUNY Upstate Medical University, Syracuse, NY; Center for Behavioral Genomics and Psychopharmacology Research Initiatives Center of Excellence (S.J.G., J.B.L.), Department of Psychiatry, University of California, San Diego, San Diego, CA; Department of Health Science and the California State University-VA Long Beach Medical Center Joint Studies Institute (R.H.F.), Long Beach, CA.

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Address correspondence to: Dr. Vural Ozdemir, Biomarker and Clinical Pharmacology Unit, VA Long Beach Medical Center, School of Medicine, University of California, Irvine, 3844 East 15th Street, Long Beach, CA 90804; e-mail: m.vural.ozdemir@gmail.com.

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Coalescence of Clinical Pharmacology and Human Disease Genetics by Shared Application of New Genomic Technologies

The scope of scientific inquiry in clinical pharmacology and human disease genetics has expanded over the past several years with the development of population-based databases (eg, UK Biobank, the Estonian Genome Project, GenomEUtwin, CARTaGENE) and the introduction of new genomic technologies, such as high-throughput analysis of gene expression.[1–5] These genomic technology platforms aim to characterize multiple genes, often on the order of tens of thousands, to enable an integrated view of genetics and its role for drug efficacy and safety. The origin of the genomic technologies is not, however, rooted in pharmacology but can be traced back to advances made on the heels of the Human Genome Project.[6–8]

Intensive deoxyribonucleic acid (DNA) sequencing efforts in the late 1990s, facilitated by the coalescence of traditional methodologies used in human genetics and cell biology, resulted in technology platforms capable of generating large volumes of data in very short time frames. Genomic technologies are now increasingly adopted in pharmacologic sciences, with an attendant expansion of the scientific process. These advances start with the view that a broader investigation of the multiple components of a complex biologic pathway targeted by a pharmaceutical compound may provide better insights into the mechanisms of drug action and ultimately allow individualization of drug therapy.[9] Hence, clinical pharmacology and human genetics research are rapidly coalescing, in part owing to such broad and shared applications of genomic technologies.

When scientific disciplines meet toward a common goal, both technical expertise and expectations of practitioners for what constitutes scientific merit inevitably struggle for position. The extent of similarities and discrepancies among the views of scientists from the respective disciplines and the ensuing critical debate on new hypotheses or technologies in a given field often serve as catalysts for the rejection or wide adoption of new hypotheses and technologies.[10] Important innovations emerge from creative interdisciplinary sharing of methods and concepts, yet it is essential that precautionary principles are adhered to in standards for scientific validity and reliability.[11–14]

Whereas clinical pharmacology is an experimental science, most genetics research on human diseases uses a scientific approach that is primarily observational. This results in an asymmetry in scientific method that can differentially impact the degree to which environmental components of phenotypic variability are controlled, including the sample size requirements of each discipline. The number of subjects participating in observational genetic studies of diseases is often used as a key criterion of attendant scientific value; it is also a significant driver of which 'disease gene' discovery is worthy of further policy-oriented translational research or application at the point of patient care. Because environmental factors (and the attendant confounding) are difficult to discern or control in observational study designs, there is an expectation, particularly on the part of the policy makers familiar with population health and large-scale epidemiologic studies, of a large sample size (eg, from several hundreds to thousands) in genetic studies on disease predisposition. Yet these requirements do not necessarily apply to experimental study designs.

Environmental confounding can (and we suggest should) be monitored more readily by scientists in experimental sciences (eg, in pharmacology or pharmacogenomics) prior to or during the execution of the study. Failure to discern such discipline-specific nuances for differential environmental confounding in genetic studies rooted in either pharmacology or disease predisposition will bias expectations for sample size requirements, along with perceptions of the merit of new genomic discoveries. Such interdisciplinary differences in norms and expectations regarding scientific merit may lead to inadvertent dismissal of methodologically sound small-scale exploratory pharmacogenomic studies as new policies are being developed for genomics research in population-based databases. Some of these pharmacogenomic studies may well have appropriate statistical power to detect genetic components of pharmacologic variability.

Pharmacogenomics is usually defined as the study of variability in drug response using information from the entire genome of a given individual patient.[1,2,4] Pharmacogenetics, by contrast, is hypothesis driven

and focuses on a limited set of candidate genes selected based on a priori observations of disease susceptibility, drug absorption, metabolism, transport, and excretion, as well as drug targets, as opposed to a genome-wide hypothesis-free approach in pharmacogenomics. It is noteworthy that pharmacogenetics and pharmacogenomics are also interdependent: once a novel gene(s) of relevance for mechanism of drug action is identified through the genome-wide pharmacogenomics search, such individual genetic biomarkers require further validation and follow-up by pharmacogenetics before they can be routinely applied in clinical medicine. For the purpose of the present discussion, we use the term *pharmacogenomics*, but many of the concepts discussed herein will also be applicable to pharmacogenetic investigations.

The objective of the present comparative analysis is to identify and elaborate on these significant asymmetries between clinical pharmacology and human disease genetics in the hybrid field of clinical pharmacogenomics. We emphasize the importance of recognizing pharmacogenomics as an experimental form of science. This broader view of pharmacogenomics addresses an ethical and science policy imperative to favor prospective clinical pharmacogenomic investigations over the ad hoc retrospective biomarker investigations that have, thus far, typified biomarker applications at the point of patient care or late-stage drug development.

Expectations and Challenges for Policy Making in Interdisciplinary Science

Expectations about the merit or promise of a biotechnology or a new scientific field evolve through a complex and subtle interaction of (1) media interest and consumer demand in the society (eg, patients, caregivers, and physicians) for better therapeutic products and services; (2) dialogue among scientists, governments, and policy makers to ensure that the latest scientific standards are met and empirically grounded interdisciplinary science policies are developed; and (3) corporate or private sector marketing of resulting technologies.

Within the process of policy making, there may be increased complexity (and unpredictable outcomes) when disciplinary boundaries are crossed by individual regulators or scientists investigating the broad application of a novel discovery or technology in multiple fields of scientific inquiry. This situation is particularly evident with the application of genomic, proteomic, or other high-throughput '-omics' technologies in fundamental and applied bioscience research. Such cross-disciplinary journeys are not without their challenges. Scientists regularly encounter stigma and resistance to novel hypotheses or methods, and collaborations can reach an impasse when the norms governing scientific merit in a discipline are not mutually reconciled or renegotiated in light of the particular attributes of each field of inquiry. Thus, while evaluating new technologies and concepts borrowed from diverse but complementary disciplines, regulators engaged in policy making need to employ multiple lenses to discern disciplinary nuances.[15–17] This is a timely consideration for, as noted earlier, many countries and the private sector in applied genomics are in the process of developing large-scale genomic databases and biobanks.[3,18,19] When drawing conclusions on the public health significance of new genetic discoveries and their potential for application in patient care, identification of the particular characteristics of human disease genetics and pharmacogenomics that strengthen or weaken the credibility of the resulting methods or products should be taken into account.

Contrast between Observational and Experimental Study Designs: Why Is This Relevant to Interdisciplinary Policy Development for Pharmacogenomics?

Since the late 1990s, the idea of exploring pharmacologic phenotypes (eg, drug effectiveness and side effects) as another promising dimension of genetic research has attracted a number of human geneticists to the field of clinical pharmacology and vice versa. This bidirectional exchange of scientific expertise benefited and complemented the classic pharmacologic approaches to questions of variability in pharmacokinetics and pharmacodynamics. At the same time, there has been a tendency to view pharmacologic responses akin to disease phenotypes. There are, however, several fundamental differences between human disease genetics research and clinical pharmacogenomics that require particular attention for a balanced interpretation of scientific merit in genetic studies of pharmacologic phenotypes (Table 1).

A fundamental goal of human genetics research is to establish the causal links between genes and disease phenotypes or characteristics. Yet most common complex human diseases initiate and progress over a considerable period of time before clinical signs and symptoms manifest. This means that environmental contributions to disease phenotypes are difficult to determine without longitudinal studies. It can be prohibitively expensive to discern disease-environment interactions when long-term observation and follow-

Table 1 Distinctions in Scientific Method (Experimental vss Observational) between the Disciplines of Clinical Pharmacogenomics and Human Genetics, Respectively, that May Differentially Influence the Sample Size Requirements and the Attendant Perceptions on Scientific Merit

Discipline-Specific Attribute	*Clinical Pharmacogenomics*	*Genetics of Common Complex Human Diseases*
Study design considerations		
Most common design	Experimental; the investigator can actively manipulate the drug dose or exposure	Observational; the investigator does not induce the disease and instead quantifies phenotypes, usually after disease is clinically manifested
Within-subject study design	Feasible	Not feasible or can be unethical
Reduction of bias in study design with use of randomization	Feasible	Not feasible; disease susceptibility is not subject to assignment and, rather, is observed
Phenotype considerations*		
Temporal attributes of phenotype	Both prospective and retrospective samplings are feasible	Often retrospective sampling of disease phenotypes is required or the only feasible option
Repeated measures data collection to enrich phenotypic characterization	Feasible	In most cases, it can be prohibitively expensive owing to long time frames required for clinical manifestation of disease signs and symptoms
Environmental contribution to phenotypes	Calculable	Often incalculable; difficult to control or eliminate when calculable
Baseline phenotypes	Discernible prior to drug administration; this allows unequivocal calculation of the net drug-related phenotypes by subtracting the predrug phenotypes from the composite phenotypes obtained post–drug administration	Often not discernible owing to slow initiation and progression of most common complex human diseases over many years
Rechallenge/challenge with independent variable (ie, drug treatment or disease induction or susceptibility)	Phenotype ascertainment and its 'drug-relatedness' can be further strengthened by discontinuation of drug treatment followed by subsequent rechallenge with drug treatment	Disease processes often cannot be experimentally switched 'on' or 'off' to ascertain the attendant clinical phenotypes
Other distinctions		
Feasibility of in vitro studies to estimate the scope of allelic or locus genetic heterogeneity	Drug itself can be used as a 'probe' by virtue of its physicochemical interactions with drug-metabolizing enzymes, transporters, or molecular targets for efficacy to discern the high-priority candidate pharmacokinetic and pharmacodynamic pathways and the attendant locus and allelic genetic heterogeneity In vitro studies are feasible to estimate the upper-bound limit on the number of plausible candidate genes, particularly in the case of pharmacokinetic pathways or molecular drug targets	Often no biologic or physicochemical probe is available to empirically discern the type or the number of disease-related biologic pathways (with the exception of certain environmentally induced cancers or diseases)

*Our comparative analyses should not suggest that clinical pharmacogenomics, as a discipline, is uniformly at a greater advantage in achieving optimal phenotype ascertainment and study design than human disease genetics research. Instead, the distinctions highlighted are context specific and emanate primarily from the differences in the scientific method between the two disciplines (experimental vs observational, respectively). Moreover, phenotypic ascertainment of certain pharmacologic phenotypes, particularly in the case of categorical treatment outcomes (eg, responders and nonresponders), can meet with discordance among physicians, whereas the availability of disease diagnostic criteria (eg, *International Classification of Diseases*) may facilitate uniformity in phenotype ascertainment in human disease genetics research.

up are required in ostensibly healthy individuals who are predicted to develop a disease phenotype in the far too distant future. By contrast, as an experimental science, clinical pharmacology is able to elicit phenotypes (in a controlled laboratory or hospital setting) within a matter of a few minutes (eg, antihypertensive drugs), days, or weeks (eg, anticancer medications), during which it is feasible to measure and account (to a certain extent) for environmental components of pharmacologic variability. Seen in this light, it is possible to understand drug effects as an acquired form of biologic variance.[20]

The measurability of drug effects and the recognition that drugs are well-characterized modifiers of normal life processes or (patho)physiologic events led, nearly 50 years ago, to establishment of the origins of pharmacogenomics as a new medical subspecialty.[1,2,9] The technical advances over the past decade have, in effect, blurred the interdisciplinary boundaries in pharmacogenomics research. For example, even though the observational and experimental nature of human disease genetics and pharmacogenomics, respectively, may allow different degrees of control over environmental influences, such disciplinary nuances are not always recognized. This recognition is important since sample size requirements to achieve an optimal signal to noise ratio for discovery of genetic markers of pharmacologic phenotypes and disease-related traits can markedly differ.

It should be stressed that reproducibility of new genetic findings in independent samples is required in both human disease genetics research and pharmacogenomics, in part owing to population-to-population differences in the type and frequency of genetic susceptibility loci for a given phenotype in the human genome. In addition, large sample sizes are often required to detect the small individual effects of numerous genes and their complex gene-gene/gene-environment interactions on drug response or disease phenotypes. We suggest, however, that a smaller sample size is sufficient for such replication studies in clinical pharmacogenomics owing to greater control of environmental confounding in pharmacologic phenotypes.

In the late nineteenth century, Paul Ehrlich proposed the presence of "chemoreceptors" on microorganisms and cancer cells that differ from the host organism—a precursor to the current concept of molecular drug targets and selective toxicity of modern medicines.[21] The presence of discernible targets suggests that drugs can serve as invaluable probes to guide the identification of plausible pharmacokinetic or pharmacodynamic biologic pathways. One concrete example is in vitro drug metabolism studies that reliably identify the CYP-450 enzymes that may contribute to clinical pharmacokinetics of a new therapeutic candidate. Because only a handful of CYP-450 enzymes are responsible for drug metabolism, these in vitro approaches can provide a practical upper-bound limit on the number of candidate genetic loci and, by extension, the scope of genetic heterogeneity causally related to variability in a clinical pharmacology phenotype.[17,22]

These theoretical and applied nuances collectively underscore the fact that environmental factors and genetic heterogeneity can be discerned or controlled more readily (although never totally controlled) in clinical pharmacogenomics than human genetics by virtue of pharmacology's nature as an experimental science (see Table 1).[23] Hence, for a given sample size, our ability to detect genetic markers may be significantly enhanced by careful consideration and accounting for environmental effects through experimental study designs in pharmacogenomics. Additionally, the application of randomized and prospective pharmacogenomic studies is an entirely feasible strategy through which confounding by environmental factors can be further reduced.

A rational strategy is needed to assign priority to drugs that are subject to a higher degree of genetic regulation.[22] This would enhance the signal to noise ratio for genetic factors and could permit pharmacogenomic association studies in smaller number of subjects. Typically, heritability estimates are obtained using the twin method. Twin studies are very useful to establish the genetic components for common complex disease phenotypes (eg, breast cancer) but have limited applicability in pharmacologic responses to drugs. Some of these limitations include difficulties in recruitment of twins and obtaining clinical outcome data in both twins (since the twin pairs may not suffer from the same disease at the same time), as well as the financial cost of twin investigations. To remedy the difficulties associated with the twin approach, a repeated drug administration (RDA) method was proposed by Werner Kalow wherein between- and within-subject variances in drug efficacy or safety are compared.[22,24,25] The RDA method requires the following considerations. In a given individual, within-subject variance (SD_w^2) is determined by environmental factors and measurement errors ($SD_w^2 = SD_{environment}^2 + SD_{measurement\ error}^2$). Notably, the second term ($SD_{measurement\ error}^2$) includes not only measurement error but also biologic variation, random and nonrandom (eg, circadian). On the other hand, between-subject variance (SD_b^2) can be formulated as

($SD_b^2 = SD_{environment}^2 + SD_{genetic}^2 + SD_{measurement\ error}^2$). As originally proposed by Kalow and colleagues,[24] the genetic component (r_{GC}) of variability in a time-dependent pharmacokinetic or pharmacodynamic occurrence can be estimated with the following equation:

$$r_{GC} = \text{Genetic component} = \left(SD_b^2 - SD_w^2\right)/SD_b^2$$

The r_{GC} values approach 1.0 point to overwhelming genetic control, whereas those close to zero suggest that environmental factors dominate. In essence, any dynamic biologic process exhibiting time-dependent decay and negligible carryover effects between repeat observations can be amenable to RDA studies to dissect the genetic contribution to interindividual variability in the corresponding biologic phenotype.[22] Recent applications of the RDA method demonstrate that genetics plays a paramount role in pharmacologic traits hitherto not subjected to pharmacogenomic analysis, such as renal drug disposition and pharmacokinetic variability of the antiretroviral drug didanosine.[26,27]

In our focused comparison of clinical pharmacogenomics and human disease genetics research, it should be clear that despite the application of prospective design, clinical pharmacogenomics cannot completely account for the diverse socioeconomic and environmental factors (eg, other medications, alcohol, diet, workplace, etc.) that will actually affect the patient and potentially result in adverse drug reactions in their day-to-day use of the medication.[28] Moreover, phenotypic measurement of drug effects remains particularly problematic in fields such as psychopharmacology, even in the presence of strict monitoring of environmental effects. The temporal and geographic plasticity of human behaviors (independent from drug treatment) and limitations of clinical rating scales to capture nuanced changes in behavioral responses to drugs introduce uncertainty in ascertainment of pharmacologic phenotypes in psychiatric pharmacogenomics.

Increased Ability to Generate High-Throughput Genomic Data Creates New Sociotechnical Actors and Control Points in the Scientific Process

High-throughput genomic technologies can generate large volumes of genetic data, but they also create a particular statistical conundrum. To attain adequate statistical power and to allow association analysis between multiple genetic factors and clinical phenotypes, researchers require an increasingly larger number of human subjects or biologic specimens (eg, biopsy material from cancerous tissue) to match the high-throughput data generated by new genomic technologies. At first glance, this may come across solely as a logistical issue concerning subject recruitment for clinical pharmacogenomic investigations. Indeed, subject recruitment is, and has always been, an important barrier to successful execution of clinical investigations, whether they are in the area of human disease genetics or pharmaceutical research. However, present throughput of the data generated by genomic methods is vastly greater, by at least several orders of magnitude, compared with only a decade ago.

Reflecting on the three key components of scientific process, from (1) conception of new ideas or study design and (2) execution of a study protocol (eg, including subject recruitment) to (3) analysis and interpretation of new findings, it becomes evident that subject recruitment or collection of clinical phenotypic data is increasingly the de facto critical rate-limiting step or bottleneck in pharmacogenomics.[29,30] The cost of genotyping or other genomic methods has declined markedly, and sophisticated but affordable bioinformatics software and trained personnel are available for association analysis to establish the link between genomic data and clinical phenotypes. This, then, invariably affects the nature of stakeholders and the attendant sociotechnical networks.[29] The role of scientists as gatekeepers in genomic science is being fundamentally altered.[29] In particular, those scientists with small-scale innovative laboratories with limited subject recruitment infrastructure are particularly vulnerable to this new type of large-scale recruitment-driven genomic science. New sociotechnical actors and research coordinators who are not necessarily grounded in human genetics, pharmacology, or social sciences may thus become influential in subject recruitment and, by extension, in research governance.[29,30]

Returning to genomics and science policy, it is noteworthy that the present emphasis on large study sample sizes in clinical pharmacogenomics in part reflects the expectations carried over from observational genetic studies on disease susceptibility as the two disciplines coalesce around shared genomic technologies. If the experimental nature of clinical pharmacogenomic inquiries and the attendant ability to better control or eliminate environmental contributions are not fully appreciated, there will be a risk of premature dismissal of small sample–sized pharmacogenomic studies, even though, as noted earlier, they may have adequate statistical power. Thus, the differences in scientific method in clinical pharmacogenomics and human disease genetics present challenges to practitioners in both research fields. There are

also, however, untapped opportunities to increase adoption and acceptance of genomic technologies at the point of patient care. In particular, the recognition that pharmacogenomics is an experimental science creates an avenue for a systematic policy response to the ethical imperative to prospectively pursue genetically customized therapies before regulatory approval of pharmaceuticals.

Visions of Pharmacology as an Experimental Science: An Ethical Obligation to Conduct Prospective Pharmacogenomic Studies?

In general, the drug development process spans between 10 and 15 years from the discovery of a new drug molecule to regulatory approval for the drug to be marketed to the public. Understandably, a lag period is anticipated before new therapeutics developed with the use of -omics technologies, such as pharmacogenomics or proteomics, will be available in the clinic. For drugs that are presently in clinical use, one might expect that pharmacogenomics would have been already adopted prospectively in phase 4 clinical trials (ie, postmarketing studies of large patient populations) as there has been a dramatic increase in the availability of -omics technologies in biomedical research laboratories over the past decade.[6,11] It is interesting to note, then, that there is an acute shortage of prospective clinical studies designed to individualize drug labels, that is, formally limit a drug's target population to those people with a certain genotype.[8,15,31]

To date, most pharmacogenomic studies have been conducted in clinical trials designed for another purpose: to demonstrate efficacy or safety for drug registration by regulatory bodies such as the US Food and Drug Administration (FDA). The highly structured time frames in these trials may not always permit adequate scientific rigor or flexibility for exploratory research oriented toward genetic test development for individualization of drug therapy. In certain cases, this may lead to an ad hoc retrospective sampling of clinical trial data (eg, only when or if a compound displays toxicity after introduction into the market), even though, as noted earlier, prospective study designs are entirely feasible in pharmacology. By contrast, an abundance of discovery-oriented research (ie, remote from direct clinical applications to customize drug therapy) with genomic technologies is taking place for identification of new drug targets or proof of concept in early-phase clinical trials.[15] But this early-phase upstream basic research does not necessarily guarantee the eventual downstream access to genetic testing or delivery of personalized medicines at the point of patient care.[15,31–33] A number of concerns, such as small market sizes in narrowly defined therapeutic fields, have been presented in the past as an explanation for the obvious trepidation associated with the prospective development of pharmacogenomic tests at the point of care.[31,32,34]

We suggest that the motivations for prospective clinical pharmacogenomic applications to proactively influence drug labels and prescriptions may also be shaped by the type of pharmaceutical associated with specific pharmacogenomic tests. In 2004, of the 113 new drug applications (ie, marketing approval) approved by the FDA, only 17 (15%) were considered significant improvements compared with already marketed products.[35] Although there is much to be celebrated in terms of singular success stories on selected innovative medicines developed by the pharmaceutical industry, many of the pharmacotherapies introduced into the market every year are 'me-too' drugs, displaying comparable efficacy and safety profiles with already existing medicines (Figure 1).[35–37] These me-too drugs may be economically very profitable and in some cases will even constitute 'blockbusters' that generate billions of dollars in revenue. But for our purposes, it is important to note that in the context of customized therapeutics, me-too drugs (whether blockbuster or not) may adversely influence motivations for pharmacogenomic testing in the clinic in ways that were previously unanticipated.

Consider a hypothetical therapeutic area (eg, statins to reduce blood cholesterol or selective serotonin reuptake inhibitor antidepressants) that is characterized by an abundance of me-too drugs, with 60 to 80% of the available drugs exhibiting a similar pharmacologic mode of action or efficacy or safety profile. A pharmacogenomic test for a me-too drug may be equally predictive of treatment outcomes for most, if not all, drugs within the same me-too category, redistributing the financial gains made on the diagnostic test from an individual pharmaceutical company holding the pharmacogenomic patent to multiple firms that manufacture similar me-too drugs. Hence, the past and present focus on me-too drug development may serve as a barrier to both innovation in pharmacotherapy and the development of targeted therapies in conjunction with pharmacogenomic tests.

Another hitherto overlooked consideration is the significant reduction over the past decade in the duration of tenure and increased turnover of chief executive officers (CEOs) in various multinational corporations. For example, in a survey of CEO succession at the world's largest 2,500 publicly traded companies, Lucier and colleagues found that 14.2% of