The role of pharmacogenetics and pharmacogenomics in improving translational medicine

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Summary

The approval of new medicines has slowed significantly over the past years. In order to accelerate the development of new compounds, novel approaches in drug development are required. Translational medicine or research, an emerging discipline on the frontier of basic science and medical practice, has the potential to enhance the speed and efficiency of the drug development process through the utilization of pharmacogenetics and pharmacogenomics. Pharmacogenetics is the study of genetic causes of individual variations in drug response whereas pharmacogenomics deals with the simultaneous impact of multiple mutations in the genome that may determine the patient's response to drug therapy. The utilization of these methods in the drug development process may therefore identify patient sub-populations that exhibit more effective responses and/or an improved benefit/risk profile upon treatment. The authors provide examples of the use of pharmacogenetics and pharmacogenomics in the fields of cardiovascular, pulmonary, oncological, and bone diseases and also highlight the potential economic value of their development.

KEY WORDS: benefit/risk profile, metabolism, pharmacodynamics, pharmacogenetics, pharmacogenomics, translational medicine.

Recently, drug development appears to be at an impasse, with delivery of new products being at an all time low. New approaches are needed to move forward. Translational medicine is one such approach, serving to bridge the divide between the laboratory and the clinic (1). This advance can help further clinical research and disease management by enabling targeted drug development.

Productivity in the development of new drugs, i.e., new molecular entities, has been flagging alarmingly. In recent years, fewer new molecular entities have been receiving marketing authorization while development costs have risen dramatically. For example, in 1997, there were 39 new molecular entities approved by the United States (US) Food and Drug Administration

(FDA) during a year when Research and Development (R&D) expenditures were estimated to be 30 billion US dollars; just 10 years later, an all-time low of 17 new therapies were approved when expenditures were over 60 billion US dollars (2).

Numerous reasons could explain the seemingly inexorable decline in productivity. For example, more challenging disease targets are now being addressed or poor choices are being made in the drug development process, allowing drug candidates to advance too far before discontinuing development. In addition, we may be evaluating candidates in inappropriate trials, or choosing inadequate dose/dose schedules before entering late stage development. Further, drug candidates may be appropriate, i.e., tolerable and efficacious, but only in a subset of patients – a patient population that needs to be identified and characterized. Lastly and perhaps more importantly, there is a failure to apply the approaches of translational medicine effectively in drug development.

Translational medicine is an interdisciplinary science that links laboratory research with clinical research. The purpose of translational medicine is to test, in humans, novel therapeutic strategies developed through experimentation. It has been described as a bi-directional pathway between the laboratory and the clinic, sometimes called "Bench to Bedside, and Bedside to Bench" (1). A recent survey suggests that one aspect of translational medicine, focusing on the genetic basis of disease with a more systematic, prospective evaluation of genetic discoveries, could enhance the development of new therapies and even overall productivity of drug development (3). The US FDA has described a similar philosophy for drug development (4, 5).

Translational research can potentially enhance drug development by helping to make the process faster, better, or less expensive, especially if you consider that most molecules entering clinical development are destined to fail (9 of 10, on average). Specifically, translational medicine may help identify failures earlier in development. Being able to identify a subset of patients who is more likely to respond to a particular drug allows one to be much more certain about the outcome of a trial if the results are either positive or negative. Improving the quality of data about a molecule that progresses to later stage development is also critical. Such data can be secured by for example: 1) ensuring that plasma levels are adequate to interact with the target (enzyme, receptor, etc.) in question; 2) understanding clearly the dose response relationship so that large scale trials employ the correct dose(s)/dose schedule; 3) identifying a patient subset who are more likely to respond to the drug, thereby allowing a higher probability of future success and a smaller sample size (fewer nonresponders, less variability in response) and minimizing the risk of safety issues in patients exposed to the molecule in question.

Pharmacogenetics and pharmacogenomics, both promising tools of translational medicine, can enhance this process. Genetics can play an important role in how patients respond to drugs. Palmer et al. categorized ways in which genetic variants may alter responses to drug by: 1) variation in metabolism of a drug among individuals; 2) variation among population members with respect to drug adverse effects that are not based on the drug's action; and 3) response or lack response by genetic

variation in the drug treatment target (6). Both pharmacogenetics and pharmacogenomics can provide these insights: the former focuses on the impact of a single gene mutation (7) and the latter on the simultaneous impact of multiple mutations that may determine the drug's efficacy and toxicity (8). Specifically, pharmacogenetics is particularly useful in understanding the ability of any individual patient to metabolize the therapeutic intervention in question, thereby improving the chances of ensuring a therapeutic plasma level of the active reagent that would interact with the target in question, or by predicting a serious idiosyncratic reaction (7, 9). In turn, pharmacogenomics is potentially important because it helps define the patients, either by their germ-line DNA or tumour DNA in the case of oncology, with the target disease entity with respect to a more consistent pharmacodynamic response to the therapeutic intervention (8). Several examples in cardiovascular, asthma, oncology, and osteoporosis areas highlight the potential improvements achieved through the application of translational medicine in the decision-making process during drug development. In these examples, the target population is enriched by identifying a more homogeneous patient population, which in turn facilitated making decisions about whether or not to proceed in later stage development with particular molecules.

The effect of genetics on how some drugs are metabolized has been known for years. Genetic variants of drug metabolizing enzymes have been identified that explain differences between individuals in drug concentrations and their corresponding pharmacodynamic, including safety, effects. The diseases and the recognized drug metabolizing enzymes have been recently reviewed comprehensively (6, 9), and involve common disorders and treatments such as depression [tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs)], cardiovascular disease (beta blockers, angiotensin 1 receptor inhibitors), thromboembolic disorders with coumarin anticoagulants; ulcer disease with proton pump inhibitors; malignant disease (thiopurines, 5 fluorouracil, irinotecan), and tuberculosis (isoniazid). However, the utility of genotyping procedures has not been consistently shown in prospective clinical trials, though a recent example evaluating the safety of the HIV therapy, abacavir, with the HLA B*5701 screening, is particularly noteworthy (9). One example where genotyping could potentially be valuable in translational research is with metoprolol and congestive heart failure (6). Both metoprolol plasma concentrations and the effects on heart rate correlate significantly with cytochrome P4502D6 metabolic phenotype, with ultrametabolizers (UM), defined as particularly rapid metabolizers of metoprolol, having a significantly lower plasma concentration than extensive metabolizers (EM) who already metabolize metoprolol rapidly. For indications such as treatment of hypertension in patients without further cardiovascular disease, the value of genotyping is more dubious because UMs and EMs can be clinically identified by monitoring blood pressure and pulse rate, but genotyping may be beneficial for longterm treatment with metoprolol in indications such infarction as congestive heart failure or in post-myocardial infarction patients where no surrogate parameter such as blood pressure is available to predict long term efficacy.

Combining a pharmacogenetic and pharmacogenomic approach with metoprolol could be particularly appealing in the setting of congestive heart failure. Several years ago, a report investigated two particular germline mutations affecting the beta 1 and alpha 2c receptors which appeared to predict excessive adrenergic activity in the myocardium and increased risk for congestive heart failure (10, 11). In the former affecting the beta 1 receptor, an Arg389 polymorphism confers enhanced intrinsic activity of the receptor which leads to greater myocardial contractility, myocyte hypertrophy, and eventually congestive heart failure. In the latter, a deletion polymorphism (Del322-

325) in the presynaptic alpha 2c receptor prevents inhibition of norepinephrine release, thereby enhancing adrenergic tone. The combination of these two polymorphisms appeared to increase the risk of congestive heart failure dramatically and presumably mediated for exaggerated sympathetic tone. Hence, and assuming these observations are confirmed, an early proof of concept study to investigate beta blockade with metoprolol in preventing left ventricular hypertrophy and with baseline hypertension or congestive heart failure in patients with baseline left ventricular hypertrophy could employ testing of both cytochrome P450 to avoid UM thereby assuring higher plasma levels and beta 1/alpha 2c variants to identify those, a relatively homogeneous population, who are at highest risk of the clinical manifestations of sympathetic hyperactivity. By ensuring consistent plasma levels of metoprolol in a subset of patients at highest risk for disease, one can make drug development more reliable and predictive, which important goals of translational research (4, 5).

The oncology area has a growing number of examples where pharmacogenomics play a particularly important role, as has been the cases for human epidermal growth factor receptor 2 (HER2) in breast cancer and epidermal growth factor receptor (EGFR) kras in colorectal cancer (12, 13). The story of gefitimib (Iressa) is particularly well-described, and the clinical observations in contrasting efficacy responses in non-small cell lung carcinoma (NSCLC) illustrate this Gefitinib is an EGFR tyrosine kinase inhibitor. It was observed that gefitimib gave a 27% response rate in Japanese patients with NSCLC, whereas the response rate of 10% in the Caucasian population seemed particularly curious (14). Further exploration of the responses in the laboratory (a case of the "bedside to bench" paradigm) helped identify mutations (around exons 18, 19, 21) in the ATP binding pocket of the tyrosine kinase domain of the receptor, which allowed for a better fit or interaction of gefitinib with the tyrosine kinase, whereas wild type tumours could not stabilize the interaction in a comparable manner (15, 16). A substantially greater percentage of Japanese patients had this particular mutation; hence their response rates to gefitinib were greater than the wild type predominant prevalence in the Caucasian population. If a "bench to bedside" approach were taken in the translational research paradigm, one could imagine a couple of different clinical investigations. First, one could seek mutant tyrosine kinase (EGFR) patient types with malignancies other than NSCLC, and evaluate gefitinib in only these subgroups. If successful in small, populations "enriched" with mutant tyrosine kinases, further evaluations could be done to allow for subsequent tumour type registrations (e.g. head and neck carcinoma [HNC]), whereas if these enriched subgroups did not respond, one could be reasonably certain that a broader population of the same anatomic location (e.g. HNC) would not respond. Alternatively, if one designed a molecule with improved binding characteristics to either the wild type or the mutant subtypes, knowing the differential responses to inhibition, one could test the relative benefits of these design changes in the appropriate groups as determined by pharmacogenomic profiling of the tumour types at the time of diagnosis.

Recently, the importance of genetics has been highlighted during the development of a new oncology therapeutic, panitumumab, for metastatic colorectal cancer. This molecule targets the EGFR in colorectal cancer.

Downstream of this receptor is a small G-protein kras. Amado et al. described how tumours expressing the wildtype variant of kras exhibited greater response to panitumumab, compared to tumours expressing the mutant variant (13).

The asthma field has revealed at least two examples of the potential value of patient genomic profiling. In the first, patients may be profiled as to their proclivity to produce leukotrienes, which are shown to be an important mediator in some patients

of the asthma syndrome. The gene ALOX5 encodes 5 lipoxy-genase; a variable number of tandem repeats (VNTRs) in the ALOX5 gene promoter decreases gene transcription, thus decreases the production of leukotrienes (17). In this particular patient subset where asthma does not appear to be leukotriene dependent, one would predict 5 lipoxygenase inhibitors to be relatively less efficacious; thus to enhance the productivity of translational research, one could exclude this patient subset from an early phase trial designed to assess the potential utility of a 5 lipoxygenase inhibitor.

The value of this genomic profiling could be in evaluating new more potent or more specific leukotriene antagonists. By enrolling patients who are uniformly more likely to respond to the antagonists, one can do early comparator trials to look for superiority or to simply use this enriched subset to understand the dose-response relationship in the phase 1 setting. Non-responder or wild type patients would make the enrolled population more heterogeneous, thereby increasing the variability of response and mandating a large sample size.

Another example in asthma relates to polymorphisms in the beta-2 receptor (reviewed in 18). Though data could be interpreted as conflicting here (19-21), the original observations posit a tendency for a certain polymorphism (Arg16/Arg16) to be associated with a less robust initial bronchodilatory response to a beta-2 agonist, along with a greater propensity for tachyphylaxis. The clinical ramifications are obvious. Patients with this polymorphism should use available beta-2 agonists as single therapeutic agents more sparingly or supplement chronic use with other bronchodilatory and/or antiinflammatory therapies. In the translational research setting, a number of questions could be addressed more efficiently by stratifying patients according to their polymorphisms: 1) what dose schedule of short-acting agents would allow for more consistent response to beta-2 agonists? 2) which patient subsets, if any, respond well to longer-acting beta-2 agonists? 3) can a diminished beta-2 pharmacodynamic response be restored by using concomitant medications such as glucocorticoids or leukotriene antagonists? (22).

Relatively little has been identified in the field of disorders of calcium metabolism and metabolic bone disease. Preliminary reports of a correlation between a polymorphism of the vitamin D receptor and bone mineral density were not confirmed by later studies (23, 24). In two reports, a polymorphism in an intron region of oestrogen receptor alpha – viewed as being associated with bone mineral density response and with HDL cholesterol response – provide a theoretical example which has potential heuristic value. In the former, a polymorphism of an intron of oestrogen receptor (alpha) seemed to be significantly correlated with an enhanced BMD response in the lumbar spine to oestrogen administered in low doses, though these data do not confirm earlier observations (25, 26). In this same region of the receptor, defined as IVS1-401 C/C genotype, polymorphisms were associated with higher HDL responses to estrogens, which is particularly intriguing since the HDL3 subfraction, that is most strongly associated with coronary events was most affected (27). Now, if one wanted to identify an oestrogen dose which would maximize bone anti-resorptive and anti-atherosclerotic, cardioprotective effects, and minimize potential proliferative effects on breast and uterine tissue, one can identify the subset of patients who are hetero- or homozygous for these polymorphism and compare the responses to various doses of oestrogens (to confirm these intermediate endpoint effects of BMD and HDL-cholesterol) and placebo. If confirmed in such a "translational research" evaluation, larger cardiovascular and skeletal endpoint studies could be performed to evaluate whether this subset of postmenopausal women would indeed have a maximal benefit-risk profile from administered oestrogens. Equally intri-guing but even more speculative, one could evaluate this particular subset of patients in small trials to assess whether selective oestrogen receptor modulators, such as raloxifene, interact in a similar manner with these polymorphisms which would then identify a group of patients who could have more robust antiresorptive and lipid effects while enjoying the benefits of breast cancer prevention.

The implications of using pharmacogenetic-pharmacogenomic testing to stratify patient groups during translational and later stage development could be substantial as a molecule becomes a registered therapeutic for a specific disease. The potential clinical benefits of identifying a subset of patients who have a greater benefit-risk profile should be considered in light of the costs of any diagnostic procedures required to identify such patients. A model has been developed which estimated the likely cost impact of using a hypothetic pharmacogenomic test to determine a preferred initial therapy (28). In the "Test All" strategy, more patients fall into lower cost ranges of the distribution. In the base case (15% phenotype prevalence, 200 US dollars test, 74% overall first line treatment efficacy and 60% second-line therapy efficacy) the cost savings per patient for a typical run of the testing strategy simulation range from 200 to 767 US dollars (5th and 95th percentile). The cost of genetic variant prevalence tests and the cost of choosing the wrong treatment are key parameters in the economic viability of pharmacogenomics in clinical practice. Thus, overall, for a genomic subset of reasonable prevalence, the cost of up front testing for all patients is likely less than or equal to the cost alternative treatment options and the cost of safety issues which accrue to the subset of patients who are much less likely to have benefits. This economic benefit is obviously in addition to the individual patient benefits of a higher benefit to risk profile upon treatment.

Pharmacogenetics and pharmacogenomics should therefore improve our ability to customize patient-specific strategies to predict, prevent, diagnose, and treat disease leading to individualized treatments.

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