

New applications of disease genetics and pharmacogenetics to drug development[☆]

Allen D Roses^{1,2}, Ann M Saunders², Michael W Lutz², Nanyin Zhang³,
 Ahmad R Hariri², Karen E Asin⁴, Donna G Crenshaw¹, Kumar Budur⁴,
 Daniel K Burns¹ and Stephen K Brannan⁴

TOMMORROW is a Phase III delay of onset clinical trial to determine whether low doses of pioglitazone, a molecule that induces mitochondrial doubling, delays the onset of MCI-AD in normal subjects treated with low dose compared to placebo. BOLD imaging studies in rodents and man were used to find the dose that increases oxygen consumption at central regions of the brain in higher proportion than activation of large cortical regions. The trial is made practical by the use of a pharmacogenetic algorithm based on TOMM40 and APOE genotypes and age to identify normal subjects at high risk of MCI-AD between the ages of 65–83 years within a five year follow-up period.

Addresses

¹ Zinfandel Pharmaceuticals, Inc., Durham, NC, United States

² Duke University Medical Center, Department of Neurology, Durham, NC, United States

³ Pennsylvania State University, Department of Biomedical Engineering, State College, PA, United States

⁴ Takeda Pharmaceuticals, Deerfield, IL, United States

Corresponding author: Roses, Allen D (roses@zinfandelpharma.com,
allen.roses@duke.edu)

Current Opinion in Pharmacology 2014, 14:81–89

This review comes from a themed issue on **Neurosciences**

Edited by **David G Trist** and **Alan Bye**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 3rd January 2013

1471-4892/\$ – see front matter, © 2013 The Authors. Published by Elsevier Ltd. All rights reserved.

<http://dx.doi.org/10.1016/j.coph.2013.12.002>

It is important when discussing genetics and pharmacogenetics [PGX] in clinical pharmacology and drug development to acknowledge the technologies that are commonly practiced in drug development. From a genetics point of view, the contents of clinical pharmacology databases for drug metabolites and PK/PD have certainly been extended by genetic/genomic technologies over the past two decades. In particular, sequencing

of highly polymorphic loci such as the HLA region and genes involved in drug metabolism have increased specificity of genetic associations with pharmacokinetic or pharmacodynamic phenotypes. This expanded compendium of polymorphisms, including less frequent polymorphisms, has increased our ability to explore the genetics of uncommon events in different ethnic groups. One example is the genetic underpinnings of the hypersensitivity syndrome observed in about 4% of Caucasian users of abacavir to treat HIV infection [1]. GlaxoWellcome received an accelerated approval to market abacavir, but approval was accompanied by an expectation by the FDA and EMA that the company would investigate the hypersensitivity syndrome. Cooperation throughout clinical development at GlaxoWellcome was necessary to undertake the experiments that would allow for the identification of the subgroup of patients for whom abacavir was contraindicated. While the HLA-B57 locus was known in 1997, from a database point of view it took several years to identify the B-5701, 5702 and 5703 polymorphisms at the locus using genomic sequencing. The risk of the hypersensitivity reaction was present only in patients with the B-5701 allele.

Today human drug trials provide opportunities to identify efficacy responders and to characterize their genetics compared to non-responders [2]. Since very large numbers of patients are usually not available [affordable or practical] as they may be for studies of risk factors for common diseases studies, the analytical process is a bit reversed from searching for genetic mutations for Mendelian disease diagnoses. Patients must be identified and followed during and after treatment. Predicting efficacy for individual patients who might also be at risk for an adverse response will take time to become common in medicine. Drug trials take years and must be designed to prospectively evaluate patient responses. A basic requirement for genetic testing is that consented DNA samples must be collected across the entire study. In reality, to accomplish collection of DNA from all study participants requires planning and patient consent, without which pharmacogenetics cannot be used effectively for hypothesis generation, hypothesis testing and for regulatory decisions.

It is a bit different for uncommon adverse events where the genetic loci associated with relatively rare, overt

[☆] This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivative Works License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

phenotypes are typically easier to identify. For safety PGX, the uncommon mutations can be assessed against population samples, but for efficacy within a trial it is necessary to study all participants so that efficacy and lack of efficacy can be compared in participants who received drug. It is, however, a problem when DNA is not collected or unavailable in individuals with adverse events. Banking DNA samples from important studies is still quite uncommon in the industry [1,14].

The goal of efficacy PGX is to find a genetic biomarker that predicts high expectation of efficacy in a sufficient number of people to qualify the test for selection of drug therapy. These studies focus on the response to treatment, and may be quite distinct from genetic diagnostic tests for disease. Beginning with any early Phase II treatment trial, the objective is to differentiate those treated individuals who respond to the drug but are not responsive to placebo. This can initially be evaluated in small studies during which defined clinical responses are measured. The more obvious the efficacy response, the more certain early associations can be made. Efficacy PGX depends on the choice of therapeutic agent, dose, and the responses of the individuals receiving the drug. It is also influenced by the type of genetic search performed. Candidate gene lists involving proposed disease pathways have provided an effective starting point for translation to clinical trials for several decades. Genome-wide association studies (GWAS) have produced many gene lists with subsequent rationales provided for selected genes. To date, there are few examples where specific genes “discovered” by GWAS lists have translated into clinically relevant programs, outside of oncology where affected tissue is more available to confirm with gene expression studies.

Each subsequent Phase II trial will provide greater statistical support for markers associated with drug efficacy. Recently, an investigation of highly polymorphic structural genes that carry highly polymorphic variations at a single locus compared to SNPs has reduced the time necessary for translation to clinical trials [3]. A high degree of polymorphic variations contribute to the proportion of individuals in a population who are informative at that locus. Efficacy biomarkers identified and validated in Phase II may be useful in proof of concept studies and to stratify and improve the efficiency of Phase III trials. PGX markers that enrich for responders in Phase III studies may allow for a more robust efficacy signal and a faster path to registration. Companion diagnostics can be also be qualified in late clinical trials to identify individuals with a higher ‘risk’ of a beneficial response [3,4]. It should also be noted that polymorphisms in one ethnic group may be absent or occur at a lower allele frequency in other ethnic groups. This emphasizes the need to examine genetic markers carefully in different ethnicities, especially with highly variable markers [5].

This short opinion piece will emphasize some of the newer genetic technologies that can facilitate Phase III trial design. Efficacy PGX is a relatively new application of genetics in clinical development because it requires DNA collection during the trial. In this new paradigm for drug development, drug discovery becomes more dependent on studies that utilize these PGX associations.

Safety PGX in the aforementioned abacavir trial demonstrates the translation of a genetic marker to ensure safer use of the medication. In addition, economics are often the major consideration for use of a test, particularly for defining efficacy for reimbursement. Predicting adverse responses also leads to extended market use in addition to enhanced safety long after patent exclusivity for the drug compound expires. In the case of abacavir it is still used in HIV drug combinations for HLA-B5701 negative patients, thereby extending its commercial value after its chemical patents expired.

New technologies and innovation in a Phase III clinical trial: trial design to study delay of onset

Central nervous system [CNS] diseases have recently experienced declining interest by major drug developers because the costs of doing clinical studies in these disease areas can be high and likelihood of approval low. The basic premise that early clinical pharmacology and safety studies can rule out [kill fast] compounds works for Phase I, but there are major differences in the cost of Phase II and Phase III clinical studies. It can be very costly to run clinical trials to observe efficacy in a dose-finding trial. This is especially true for longer trials with clinical endpoints followed over months, such as those performed for neuropsychiatric disorders.

Studying clinical pharmacology in animals and translating these findings into human studies is critical for generating information on dose and trial design that can translate into reducing overall drug development cost and time to approval. Imaging technologies have now been applied to measure effects of different drugs and drug doses on the pharmacodynamic response of specific anatomical areas in the brain. While drug dosages are usually pushed to the highest tolerated level to ensure that efficacy will not be missed, the chances for adverse events are raised as well. For neurological diseases, imaging studies in animals provide a way to determine the most reasonable, effective dose without waiting for expensive clinical efficacy studies to define it.

PET and fMRI imaging studies in animals and man can now be used for dose finding studies in late discovery and early development, particularly in the neuropsychiatric diseases from which major pharmaceutical companies have generally withdrawn over the past five years. These data can quickly and economically define the lowest dose

Download English Version:

<https://daneshyari.com/en/article/5826096>

Download Persian Version:

<https://daneshyari.com/article/5826096>

[Daneshyari.com](https://daneshyari.com)