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Pharmacogenetic and Pharmacogenomic Studies

Impact on Drug Discovery and Drug Development

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Abstract

The topics discussed in this article are concerned with studying genomic polymorphism and identifying new therapeutic targets, the role of genetics in preclinical and clinical drug development, and cultural, regulatory and logistical aspects of the development of pharmacogenetics in France. The conclusions are that from a physiological, biochemical or genomic point of view, the study of human genetic polymorphism has obvious potential value for drug development, because it can help to identify new therapeutic targets, and to predict drug efficacy and tolerability more effectively. There are already several examples of the latter approach, which relies on studying the genetic variability of enzymes involved in drug metabolism, and that of the effector molecules of the pharmacological activity. Pharmacogenetics could eventually make it possible to personalise drug treatments, as methods for analysing genes are simplified and their cost reduced. To help attain this still far-off goal, certain recommendations have been proposed.

Keywords: pharmacogenetics, genome, drugs

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1. Introduction

The development of methods for studying the genome has generated a considerable amount of 'anatomical' information about the sequences of genes and the interindividual variation in these sequences. Other studies have concentrated on simple or more complex physiological phenotypes, such as susceptibility to developing certain diseases, and have shown the existence of hereditary influences on these phenotypes. The two approaches are complementary and combining them has made it possible to identify the molecular basis of the polymorphism of these phenotypes in a certain number of cases and to establish the physiological consequences of interindividual variation in the sequence of the genome. This field is concerned in principle with drug development and several stages of such development. Indeed, by contributing to the identification of pathogenic genes and others genes that have a role in protecting against the development of certain diseases, it constitutes a possible approach to identifying new drug targets. Furthermore, there can be variation in the genes encoding the enzymes involved in drug metabolism and the molecules that are pharmacological targets. Study of this variation can help to predict drug efficacy and tolerability at the population or individual level. These concepts are important and this field of research is progressing rapidly. Its value in drug development has been analysed during the sessions of this round table.

2. Studying Genomic Polymorphism and Identifying New Therapeutic Targets

A strategy for searching for therapeutic targets by studying human genetic polymorphism and its association with certain diseases is currently progressing, with substantial resources, in sev-

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eral pharmaceutical groups and generally in collaboration with academic research scientists and clinicians. It relies on biological concepts that help to identify the molecular basis of human genetic polymorphism. Current data show that, as well as the basic model in which an allele is associated with a phenotypic feature, it is important to consider more complex but more powerful models of multigenic heredity (underpinned by the complexity of the phenomena of heterogeneous alleles and loci, haplotypes and interactions between genes) in defining physiological phenotypes and in the development of disease.

This approach relies on studying the DNA of groups of affected patients or families in order to identify the genes involved in the development of the disease, and seeking potential therapeutic targets among these candidate genes. This can be particularly valuable in diseases for which there is neither a good experimental model of the disease nor a strong pathogenic hypothesis, such as neuropsychiatric diseases.

Although this strategy has a solid theoretical basis, it should be emphasised that it has met with certain difficulties during its development, and that at present it is impossible to assess from the point of view of the pharmaceutical industry. One of the practical difficulties for manufacturers is access to patients, and another is the fundamental problem of the quality of the phenotyping of the cohorts, which ultimately determines the validity and the value of the results. This strategy of identifying targets on the basis of studies of genetic association can result in drug development only in the long term. This is due to the fact that sufficient proof must be obtained by replicating studies, incorporating complementary data from different approaches (animal models, studying the transcriptome), and choosing possible candidates for pharmacological intervention from the pathogenic or protective genes identified.

Whether they are conducted in academic laboratories or pharmaceutical industry laboratories, studies of genetic association also have considerable intellectual value, which poses a problem for manufacturers with regard to the communication of their results.

In conclusion, it appears to be important that manufacturers should continue to favour these long-term strategies, which are promising but will be difficult to evaluate for several years in terms of discovering new drugs.

3. Pharmacogenetics and Preclinical and Clinical Drug Development

The importance of genetic factors in the variability observed between individuals in their response to drugs and the risk of toxicity has been clearly demonstrated in several cases, particularly regarding drug metabolism by cytochromes P450, and azathioprine and abacavir toxicity.[1-3]

It is highly desirable that pharmacogenetic studies should develop further and that the value of molecular genetic analyses for drug prescribing should be assessed, in particular for common diseases such as cardiovascular and psychiatric diseases, diabetes and cancer.[3-7] There can, however, be several obstacles to such development:

- Conceptual: The attitude of research scientists and doctors, who seek in principle to personalise treatment on the basis of scientific hypotheses, can conflict with that of the manufacturers and organisations that finance healthcare, as the latter prefer the apparently simpler approach of prescribing directly without increasing the number of laboratory tests. The pharmaceutical laboratories have, however, made great efforts in this field, and there have been major strategic moves towards furthering the development of pharmacogenetics during the various phases of clinical studies on drugs.
- Scientific: In this regard, there is insufficient knowledge about the factors involved in drug metabolism, their genetic variability, and the genetic variability of the molecular targets of the various drugs. One important point is that the value of studying genetic variability that has already been identified or the variability that will be identified in the future should be assessed by interventional clinical trials designed to answer this question, and should not be left solely to pharmacokinetic and tolerability studies. It would be necessary, for example, to use clinical trials to assess the value of determining certain polymorphisms of the cytochromes P450 with respect to prescribing oral anticoagulants;[8] or genetic polymorphism in the levels of angiotensin-converting enzyme with respect to cardiovascular and renal disease prevention by using inhibitors of this enzyme.[9,10] Furthermore, a new field of pharmacogenetics is developing, namely, the study of the cellular transcriptome, to analyse and perhaps personalise therapeutic responses at the molecular level.

The recommendations derived from these discussions are repeated at the end of this article.

4. Cultural, Regulatory and Logistical Aspects Affecting the Development of Pharmacogenetics in France

In France, human genetic research is controlled by legislation and regulations that govern clinical research, the collection and storage of DNA samples, and the creation of computer files. These rules, which aim to ensure compliance with codes of ethics and protection of individuals, can, in some cases, be perceived as

limiting the development of genetic and pharmacogenetic studies in France. New laws are expected soon in this field. These are actually concerned with the rules governing the wording on informed consent forms and patient information sheets for DNA sampling, in order to define the extent of the analyses that may be carried out on these samples. The way the French ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale [CCPPRB]) interprets these rules is generally restrictive, and they do not allow DNA samples to be used outside of the study originally planned, whereas advances in science and the value of biomedical research could justify new investigations. The current scope of the law dated 20 December, 1998, known as the Huriet-Sérusclat Act,[11] does not appear to be wholly suited to genetic studies. In addition, the manufacturers stress the close relationship that exists between carrying out pharmacogenetic studies and pilot, prospective and international clinical trials, which are usually conducted under strict time constraints. The delays involved in obtaining the various authorisations are long and somewhat incompatible with the dynamics of prospective trials; this raises fears that clinical trials involving genetic studies will be conducted in other European countries instead.

From the logistical point of view, biological resource centres will soon be established where DNA collections may be stored, and these will assist the development of research in pharmacogenetics. For practical reasons, certain manufacturers would, nevertheless, prefer to continue managing their own collections, while complying with the rules of ethics and French and international legislation.

5. Conclusions and Recommendations

The study of human genetic polymorphism has obvious potential value for drug development, whether for identifying new therapeutic targets or for predicting drug efficacy and tolerability. Pharmacogenetics ultimately has the potential to enable drug treatments to be personalised, including treatments for the most common diseases,[12-15] particularly because of the development and simplification of methods for analysing gene polymorphism, and their consequent reduced cost.

In order to assist in reaching that still far-off goal, certain recommendations can be made:

- Attempt to identify the enzymes that metabolise these drugs at an early stage in their preclinical and clinical development; study the genetic variability of these enzymes, as well as the variability in their pharmacological targets; and establish as far as is possible the relationship between genotype and phenotype.
- Assess the value of genetic testing, not only during pharmacokinetic and tolerability studies, but also by using interventional clinical trials designed to answer this question.
- Establish DNA banks in large interventional clinical trials and analyse the endpoints and the effect of the treatments with respect to the polymorphism of the genes that are potentially involved in the therapeutic effect and in the physiological counter-regulation.
- Improve logistics and regulations with respect to human genetic studies: develop biological resource centres for storing DNA banks, while also taking into consideration the wishes of manufacturers to manage their own DNA collections. Reconsider the procedures for setting up genetic studies and the rules governing the wording on informed consent forms regarding DNA samples, in consultation with the French ethics committee (CCPPRB) and the French agency for the sanitary safety of health products (Afssaps [Agence française de sécurité sanitaire des produits de santé]), in order to enable wider use of these samples while still complying with the rules of bioethics and confidentiality.

Participants

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