Louvain centre for Toxicology and Applied Pharmacology

Human pharmacogenomics or the promises of a personalized medicine
Clinical and experimental studies of the influence of genetic polymorphisms on the metabolism of drugs.

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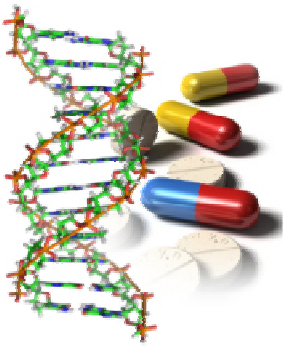

INTRODUCTION

The completion of the human genome sequencing has led to the identification and the mapping of thousands of genetic variations across the genome. Turning these variations into useful marker of drug response is the goal of pharmacogenomics (PGx). The ultimate goal is to propose an optimized treatment for every patient based on its genetic background [Fig.1]. More precisely, the PGx activities developed in our centre are focusing on drugs with a narrow therapeutic index that have complex and variable response among patients. In that way, several *in vivo*, as well as *in vitro*, studies have been implemented to assess the impact of genetic variants on the pharmacokinetic comportment of key drugs like immunosuppressants (cyclosporine, tacrolimus, mycophenolate and everolimus), antiretrovirals (lopinavir, ritonavir, saquinavir, atazanavir, amprenavir, indinavir, nelfinavir, tipranavir, darunavir, nevirapine, efavirenz, etravirin and maraviroc) or anti-cancer drugs. Particular emphasis is accorded to single nucleotide polymorphisms (or SNPs) which are single base variations across all genome. Particularly, our team is focusing in genes coding for proteins involved in absorption, distribution, metabolism and excretion (ADME) of drugs. These mechanisms are known to show inter-individual variabilities and, therefore, make good candidates for PGx.

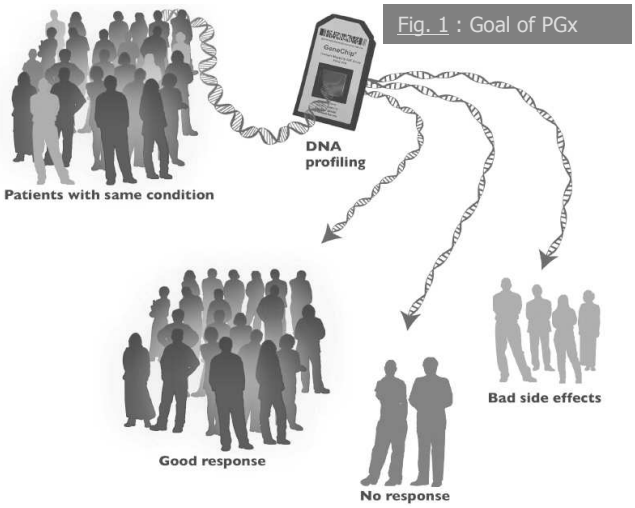

Fig. 1 : Goal of PGx

CLINICAL STUDIES

• Our center has launched prospective and transversal hypothesis-driven studies to assess the influence of genetic polymorphisms in biotransformation enzymes (e.g. *CYP3A4, CYP3A5, CYP3A7* or *CYP2B6*) or transporter proteins (e.g. *ABCB1, ABCC1, ABCC2, SLCO1B1*) on :

i. The pharmacokinetics and/or pharmacodynamics of immunosuppressive drugs in renal and hepatic transplantation [Fig.2].

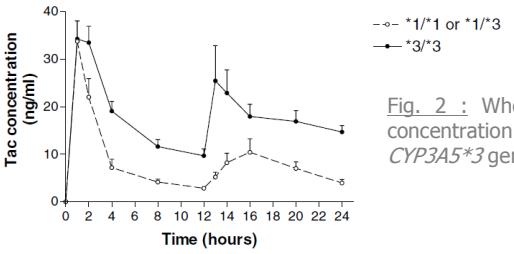

Fig. 2 : Whole blood tacrolimus concentration according to *CYP3A5*3* genotypes.

ii. The pharmacokinetics and/or pharmacodynamics of anti-HIV drugs in HIV-infected patients [Fig.3].

In a near future, our centre plans to design Genome-Wide Association Studies (GWAS) in a way to identify new genetic markers of drug response and to better understand the wide inter-individual variability observed in the response to selected drugs (post-doctoral collaboration project).

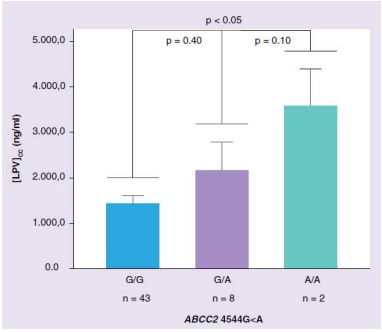

Fig. 3 : Mean Lopinavir concentration in lymphocytes ($[LPV]_{CC}$) of HIV infected patients according to *ABCC2* rs8187710G>A genotype.

Typically, these results can be of great interest for the management of patient care. As an example, one could prospect to decrease the lopinavir dosage among patients characterized by a high degree of lopinavir PBMCs accumulation, i.m. carriers of the mutation, and in this way limit systemic drug toxicity.

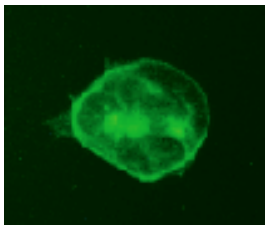

Fig. 4 : Recombinant cell clone overexpressing mutant ABCC2.

EXPERIMENTAL STUDIES

While clinical studies are critical to screen potential genetic associations, *in vitro* models may be useful to corroborate and further explain these relationships. Our studies focus on :

• The generation of *in vitro* recombinant cell models overexpressing mutant and wild type proteins. One major potential target are efflux pumps like ATP binding cassette (or ABC) transporters [Fig.4].

• Kinetics experiments on recombinant models to assess the possible activity of these efflux proteins on the cellular accumulation and the efflux of drugs.

• The impact of genetic polymorphisms on protein efflux activity towards their substrates.

These models have already allowed validating observations made *in vivo* concerning the influence of rs8187710 in *ABCC2* on the efflux of lopinavir across cell membranes.


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