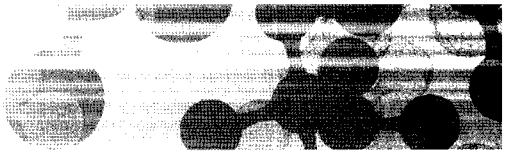

S8-4

Pharmacogenomics of Drug Disposition for the Personalized Pharmacotherapy

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Individual variation in drug response is a core issue in the area of pharmacotherapeutics and of a drug development. The pharmacological response variation may cause therapeutic failure or adverse drug reactions in patients who have unusual genotype. It has been well known that the inter-individual variation of the pharmacological responses might be caused by the heterogeneity of the disease and other clinical variables such as age, gender, diet, drug-drug interactions, and hepatic and renal dysfunction etc. In addition to these environmental factors, it is clear that genetic factors also contribute to the individual variation of drug responses of therapeutic agents, in both pharmacokinetic and pharmacodynamic phases.

The pharmacogenetic variation of drug disposition causes wide variation of drug concentrations in plasma and probably in the action site, which is usually related to the genetic difference of drug metabolizing enzymes and/or drug transporters. The drug metabolizing enzymes, in particular cytochrome P450 enzymes play a pivotal role in the elimination of many therapeutic drugs. The genetic variation of drug metabolizing enzymes may cause extensive individual variation of plasma drug concentrations, which is related to the variable therapeutic effect and toxic side effect among patients who took same dose of therapeutic drugs. Drug transporters that are highly expressed in many tissues including GI tract, hepatobiliary and renal tubular cells determine absorption, distribution and/or elimination of their substrate drugs. It is not surprising that the genetic difference of drug transporters also related to the individual variation in the disposition of their substrate therapeutics. These pharmacogenetic variations also happen among different ethnic subjects. Both genetic and environmental factors seem to influence on the ethnic difference of drug disposition.

At the moment, pharmacogenetics/pharmacogenomic principles are already applicable to the personalized pharmacotherapy in the clinical practice although it is very confined to some of well-known genes such as CYP2C9, CYP2C19, CYP2D6, TPMT, and several genes. It is expected that the genotype guided pharmacotherapy become core principle of pharmacotherapeutics, especially in the drug disposition responses in the near future.