

IN THIS ISSUE

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UGT1A1 genotype and irinotecan disposition and toxicity

The metabolism of irinotecan involves sequential activation to SN-38 and detoxification to the pharmacologically inactive SN-38 glucuronide. Previous results have demonstrated the role of UGT1A1 in the glucuronide of SN-38 and a significant correlation between *in vitro* glucuronidation of SN-38 and UGT1A1 gene promoter polymorphism. Results from Iyer *et al* (pages 43–47) suggest that screening for UGT1A1*28 polymorphism may identify patients with lower SN-38 glucuronidation rates and greater susceptibility to irinotecan-induced gastro-intestinal and bone marrow toxicity.

SULT2A1 pharmacogenetics

SULT2A1 catalyze the sulfate conjugation of dehydroepiandrosterone as well as other steroids. In their paper, Thomae *et al* (pages 48–56) have resequenced SULT2A1 using 60 DNA samples from African-American and 60 samples from Caucasian-American subjects and observed that common genetic polymorphisms for SULT2A1 can result in reductions in levels of both activity and enzyme protein. They also raise the possibility of ethnic specific pharmacogenetic variation in SULT2A1-catalyzed sulfation of both endogenous and exogenous substrates for this phase II drug metabolising enzyme.

Antigen modulates molecular mechanism of aluminum phosphate adjuvant

Adjuvants play an important role in stimulation of the immune response to

antigens, though very little is known about the molecular mechanisms of this stimulation. Regnström *et al* (pages 57–64) address this issue by studying the gene expression profiles from spleen lymphocytes after *in vivo* immunization of mice with a clinically relevant vaccine, tetanus toxoid formulated with aluminium phosphate as adjuvant, or the adjuvant alone. They conclude that the antigen modulates the molecular mechanism of the aluminium and that the identified genes may serve as predictive biomarkers in the development of new adjuvants and vaccines.

Pharmacogenetics of the arylamine N-acetyltransferases

The arylamine N-acetyltransferases (NATs) are involved in the metabolism of a variety of different compounds that we are exposed to on a daily basis. Many drugs and chemicals found in the environment, such as those in cigarette smoke, car exhaust fumes and in foodstuffs, can be either detoxified by NATs and eliminated from the body or bioactivated to metabolites that have the potential to cause toxicity and/or cancer. NATs have been implicated in some adverse drug reactions and as risk factors for several different types of cancers. As a result, the levels of NATs in the body have important consequences with regard to an individual's susceptibility to certain drug-induced toxicities and cancers. The review by Butcher *et al* (pages 30–42) focuses on recent advances in the molecular genetics of the human NATs.

COMT genotype and modafinil response in narcolepsy

The gene for catechol-O-methyltransferase (COMT) plays a key modulatory role

in dopaminergic and noradrenergic neurotransmission. Recent evidence suggests that modafinil as other stimulants might act through the dopaminergic system. Dauvilliers *et al* (pages 65–68) confirm that COMT genotype distribution between men and women narcoleptics is associated with response to modafinil. In addition, the optimal daily dose of modafinil is approximately 100 mg lower in women narcoleptics and lower in all narcoleptics with low activity COMT genotype. Our results suggest that a sexual dimorphism in COMT activity affects the response to modafinil and probably to other dopaminergic stimulants.

Pharmacotherapy prospect in type 2 diabetes

In the Clinical Implications section, Sesti (pages 25–29) investigates the results of studies of functional and positional candidate genes predisposing to type 2 diabetes, focusing on those that may influence the variability in patients' response to antidiabetic drugs or may be targets for pharmacological intervention.

Pharmacogenomic-guided drug development

The explosion of interest in pharmacogenomics and pharmacogenetics has raised concerns that the regulatory environment could inhibit progress. Lesko and Woodcock (pages 20–24) provide a regulatory perspective on the clinical studies issues and considerations, many of them currently unresolved, that pharmacogenetics and pharmacogenomics present to drug development and regulatory decision making processes.