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Getting there

In an effort to change the quality of pharmacotherapy and healthcare worldwide, an FDA- and industry-sponsored workshop was convened last April. In a summary of events, meeting co-chairs Salerno and Lesko (pp 78–81) detail the progress in creating a positive regulatory atmosphere to foster personalized medicine. About 500 registrants attended lectures on the benefit/risk ratio in implementing pharmacogenomic treatment, improving clinician education, opening communication channels between researchers and regulators, and overcoming other barriers to implementation. Six track sessions featured case studies that focused on the workshop's broad range of topics, and the results of two of these sessions are addressed in accompanying reports.

Profiles and biomarkers

Last April's third annual meeting of industry, government agencies and academics produced several discussions on how to reach the next level in this growing field. Wang and co-workers (pp 82–88) present dialogue about the use of biomarkers in prospective studies to establish a drug's efficacy. Approaches to validating biomarkers for clinical outcomes and linking the statistical results of pharmacogenomic signatures were also discussed.

At the same meeting, breakout sessions provided hypothetical situations for discussion. One session used two case studies to demonstrate how profiles can be used in all phases of drug development. Trepicchio *et al.* (pp 89–94) present examples to encourage discussion about study design, how these designs affect product labeling, and the requirements for validating pharmacogenomic classifiers. The consensus of the group was that the use of biomarkers and profiling can vastly improve Phase III trials.

BDNF's dual role

Over 1.5 million Americans suffer from Parkinson's disease (PD) – a debilitating neurodegenerative disorder that affects dopamine-producing cells. Fumagalli and co-workers review (pp 95–104) BDNF's dual role as protector and modulator in the treatment of PD. In the frontal/prefrontal cortex and hippocampus, BDNF acts as a neuroprotectant in immunophilic, herbal and cannabinoid therapies. In the substantia nigra, BDNF is a neuromodulator in dopaminergic, glutamatergic and nicotinic treatments. The authors also assess exogenous BDNF delivery, which although promising, is difficult to administer. They speculate that a treatment regimen involving a healthy diet, exercise and pharmacotherapeutics may halt or prevent the progression of PD.

CYP3A survey

Thompson *et al.* (pp 105–114) present new data to finish the first complete survey of the *CYP3A* human locus. CYP3A proteins play a large role in drug metabolism. *CYP3A* genes are expressed in the GI tract, liver, and kidney and their expression levels vary greatly within and between ethnic groups. Between all four *CYP3A* genes, 224 polymorphic sites were found. Based on patterns of linkage disequilibrium and site conservation across species, many of the variants are believed to have functional effects. The authors' findings set the stage for future association studies exploring the impact of polymorphisms throughout the locus and the incidence of breast or prostate cancer.

Quit smoking

There are approximately 1.2 billion smokers around the globe. For those who want to quit, their nicotine cravings and withdrawal symptoms can complicate the design of smoking cessation programs. CYP2A6 is the primary enzyme that metabolizes nicotine and *CYP2A6* genotypes are directly related to nicotine dependence. Kubota and co-wokers (pp 115–119) classified several genotypes as a high enzymatic activity group, which was associated with stronger nicotine dependence and worse withdrawal symptoms than a low-activity group. The first to evaluate the time to first cigarette of the day, the authors also reviewed the actual time of the first cigarette in this high-activity group. They also discuss how nicotine receptor activation may also result in more severe withdrawal symptoms in this group. Successful smoking cessation may involve more than just a patch and include pharmacogenomic strategizing.

ApoD and schizophrenia

The evidence that links lipoproteins, particularly Apolipoprotein D (ApoD), in the brain and schizophrenic disorders has been growing, but no causal relationship has yet been shown. Hansen *et al.* (pp 120–125) investigate two SNPs in the *ApoD* gene, *rs7659* and *rs1464505*, and their relation to developing schizophrenia or to long-term treatment outcomes. Studying 343 schizophrenic patients and almost the same number in controls, the authors determined that neither SNP was associated with susceptibility to the disease. However, variations at the rs7659 locus were associated with erratic treatment outcomes. The authors conclude that ApoD is not a disease marker for schizophrenia, but affects response to antipsychotic treatment in chronic patients.

Cannabis and cocaine

Cannabinoids are known to be related to both schizophrenia and a vulnerability to cocaine addiction, and several studies connect the CNR1 gene (which codes for cannabinoid receptors) to both conditions. Ballon *et al.* (pp 126–130) studied nine types of (AAT)*n* triplet repeat polymorphisms located near CNR1 in a male African-Caribbean population of cocaine addicts. In particular, (AAT)12 repeats were present in higher rates for cocaine addicts than the control group, suggesting a link between the polymorphisms and developing a cocaine addiction. The authors also note that while alcoholism was unrelated to schizophrenia in the cocaine addicts, significantly more of the schizophrenic, than non-schizophrenic patients, were addicted to cannabis, supporting a possible relationship between cannabinoid receptors and cocaine addiction.

Weighty issue

Clozapine is often prescribed for treating schizophrenia in which other antipsychotics do not work. While clozapine is lauded for not causing motor-skill related side effects, it does cause metabolic side effects, particularly type II diabetes. To learn more about the drug's mechanism of action, Sondhi and co-workers (pp 131–140) used cDNA expression array methods to identify gene expression in the brains of clozapine-treated rats. The authors confirmed an upregulation of glucose-dependent insulinotropic polypeptide (GIP) – the expression of which had not been found previously in the brain – and also in the small intestine and plasma. Though no mechanism of action was clearly identified for clozapine's affect on GIP expression, the scientists have determined that this antipsychotic drug is linked to weight gain, high cholesterol and diabetes.

Asthma targets

Asthma-related deaths, due to blocked airways and an abundance of mucus secretion, continue to rise each year. Follettie and co-workers (pp 141–152) monitored lungs in mouse models to compare gene expression after treatment with IL-13 (an asthma phenotype) and ovalbumin. Profiles of the two were similar and consistent with the finding that both induce similar asthma phenotypes. Tests reveal that both models induced gene expression in the components of the complement cascade especially C3. These studies will allow for a better understanding of the genes related to asthma and the potential molecular therapeutic targets.