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EDITORIAL

Gene array screening for identification of drugs with low levels of adverse side effects

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One of the success stories of modern toxicology is the identification of gene expression patterns that are associated with specific toxic mechanisms (Ellinger-Ziegelbauer et al. 2008; Sano et al. 2009; Dika Nguea et al. 2008). A well-known example is the classification algorithm differentiating between genotoxic and non-genotoxic liver carcinogens as opposed to non-carcinogens (Ellinger-Ziegelbauer et al. 2004, 2005, 2008). However, many more compounds or classes of compounds have been shown to be associated with specific gene expression patterns (Tsukue et al. 2009; Schug et al. 2008; Glahn et al. 2008; Hewitt et al. 2007). In this issue of the Archives of Toxicology, Jeffrey F. Waring et al. from Abbott Laboratories present another example of high practical relevance (Waring et al. 2010). In recent years, protease inhibitors have contributed to the reduction of the morbidity and mortality caused by AIDS. These protease inhibitors block cleavage of the gag and gag-pol protein precursors that are required for HIV virus maturation. However, these drugs are associated with adverse side effects. For example, results from clinical studies show an increase in cholesterol and triglyceride levels. Therefore, Waring and colleagues have administered protease inhibitors, which either cause lipid elevations or are relatively lipid neutral. Analyzing gene expression patterns in the liver of exposed rats, they identified increased expression of genes encoding proteasomal subunits specifically in the rats exposed to protease inhibitors known to cause lipid elevations. Based on this observation, the authors specifically screened for protease inhibitors that do not induce the proteasomal genes. Their efforts led to the identification of a novel protease inhibitor, which did not upregulate proteasomal marker genes and, therefore, may represent a "lipid neutral" compound. It will be very interesting to see whether this prediction can be confirmed in clinical studies.

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