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Preface

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Since the dawn of civilization, humans have feared the unknown risks associated with the use of new natural herbs or other natural medications to cure their pain, aches and illnesses. In the ancient Indian Ayurvedic Medicine which is over 4000 years old, the "Visha (poison) Tantra (wisdom)" was developed as a discipline of medicine encompassing Toxicology and Preventive Medicines. Visha Tantra included the study of various toxic herbs and animals like snake, insects, etc. and their antidotes as well as the biomarkers of toxic effects. In the Visha Tantra and the practice of Ayurvedic medicine, there have been objective descriptions of the changes in color and amount of urine, changes in the color of nails, skin, and eyes, breathing patterns, gastrointestinal disturbances, and precautionary measures to prevent adverse effects as biomarkers of toxicity associated with the use of herbal medicines and certain foods. This is probably the first description of the use of biomarkers in diagnosing diseases and adverse effects associated with therapies.

The adverse effects are inevitable outcome of the environmental and industrial chemicals and pharmaceuticals; however, efforts are ongoing to better diagnose and prevent unexpected life-threatening toxicities and/or irreversible organ damage. The search for non-invasive biomarkers that can be objectively linked to adverse effects associated with man-made synthetic chemicals including pharmaceuticals and environmental pollutants is becoming an important priority for academicians, federal agencies, pharmaceutical companies and chemical industry. Unlike preclinical toxicology studies where definitive assessment regarding toxicity and organ damage can be established using a variety of invasive histopathology procedures, the clinical safety and toxicity assessments in humans are based mostly on limited non-invasive methods (e.g., cardiac ECG, clinical pathology tests and physical exams). This has stimulated an extensive search for interspecies bridging biomarkers of toxicity and safety that may have prognostic and diagnostic utility in monitoring safety in humans exposed to pharmaceuticals and environmental agents.

Traditionally, safety assessment has relied heavily on blood and urine clinical pathology based biomarkers of toxicity. The measurement of serum based biomarkers such as transaminases (liver toxicity), serum levels of urea nitrogen and creatinine (kidney toxicity), serum creatine phosphokinase (muscle damage) has generally served well to diagnose significant adverse effects; however, these biomarkers have little prognostic value. Recently cardiac muscles specific troponins, ECG, echocardiography measurements have been used as biomarkers to diagnose cardiac toxicity and their use in monitoring cardiac health effects are on rise. It is increasingly being realized that early predictive biomarkers are needed in both preclinical and clinical drug development as well as for monitoring the adverse effects associated with environmental pollutants and pharmaceuticals exposure. Toxicity biomarkers development for assessing clinical safety poses significant problems since toxicity may not be directly related to the known mechanism(s) of action and other factors such as diet/nutrients, patient-specific diseases, and concomitant use of other drugs may contribute significantly to unexpected toxicities. In the early discovery of drugs, toxicity biomarkers can sig-

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nificantly help in identifying early and late occurring toxicities and this can be an invaluable help in prioritizing compounds based on their safety profiles. In this regard, the microarray and genomic technologies, proteomics and metabolomics/metabonomics are being successfully utilized to improve efficiencies in bringing better drug molecules forward for expensive preclinical and clinical testing. In the preclinical testing where toxicity is largely based on histopathology, noninvasive interspecies bridging biomarkers that correlate well with minimal or mild histopathology based toxicity end points are being developed. Biomarkers of drug-specific mechanisms of toxicity can be incorporated in drug development to increase confidence in evaluating drug safety in clinical settings. With better biomarkers to monitor early safety and toxicity in clinical trials, the traditional use of safety margins in clinical drug development can be improved. This will also reduce the uncertainty in extrapolation of toxicity data from animals to humans. In order for any toxicity biomarker to be acceptable extensive biological validation and bioanalytical method validation will be required. Overall, toxicity biomarkers will provide better tools to monitor important adverse effects in humans exposed to pharmaceuticals and industrial and environmental chemicals.

The present issue of Disease Markers is being devoted to toxicity biomarkers of target organs of toxicity and molecular epidemiology. The invited guest articles provide a comprehensive review of a wide spectrum of biomarkers, including molecular epidemiology biomarkers of aflatoxin and hepatitis B virus induced hepatocarcinogenesis, cytokines as the biomarkers of hepatocellular injury, application of toxicogenomics in identifying hepatic injury, drug-induced vascular injury, nephrotoxicity and reproductive toxicity biomarkers. It is our hope that the readers of Disease Markers will benefit from the comprehensive articles on biomarkers of toxicity. The editors of this special issue wish to express their gratitude and thanks to all contributing authors and the editorial staff for making this special issue a success. We welcome comments from our readers on this special issue.