tion of gene expression profiles that predispose an individual to greater adverse effects of xenobiotics. Presenters will address gene expression as a means to discover mechanisms of toxicity and/or targeted pathways that would not have been evident if standard functional assays were used in isolation, and how gene expression can be used to screen chemicals for skin sensitization potential and explain differential susceptibility to dermal sensitization or demonstrate systemic immune effects following exposure to inhaled metals. The influences of host genotype on inflammatory responses to environmental factors such as ozone and particulate materials will also be discussed.

2145 USE OF MICROARRAYS TO INVESTIGATE MECHANISMS OF IMMUNOTOXICITY.

S. B. Pruett. *Cellular BIology & Anatomy, LSU Health Sciences Center, Shreveport, LA.*

Mechanistic risk assessment for cancer has proved to be very useful and has allowed more realistic evaluation of risks for compounds that cause cancer in rodents by mechanisms that are not operative in humans. However, mechanistic risk assessment has not been actively pursued with regard to immunotoxicology end points. As genomic data are considered along with functional parameters used to screen for immunotoxicity, we will obtain information on both their predictive value as screening tools and their ability to identify potential mechanisms of action. Several practical issues must be considered in conducting such studies, including but not limited to: selection of a microarray platform, use of a purified cell type vs. whole organ homogenates, use of animals or cells that are or are not challenged to induce an immune response prior to analysis, the number of replicates needed, whether samples should be pooled or not, and whether confirmation by other methods is required. A study investigating the mechanisms by which ethanol inhibits innate immunity to bacteria in mice provides an example indicating that microarrays can provide mechanistic clues that would be difficult to obtain in any other way. Preliminary data suggest that following exposure to ethanol, similar changes in gene expression are observed in both stimulated and non-stimulated macrophages. Finally, the use of microarrays to develop a systems biology approach to immunotoxicology would seem to now be feasible, and this may allow generalizations and predictions of immunological effects not possible at the present time. This work was supported by grants from NIEHS and NIAAA.

2146 IDENTIFICATION AND PRIORITIZATION OF GENE EXPRESSION CHANGES IN DENDRITIC CELLS AS A SCREEN FOR CONTACT ALLERGY.

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Allergic contact dermatitis (ACD) resulting from skin exposure to sensitizing chemicals is a common occupational and environmental health problem. A critical step in the induction of ACD is the uptake and processing of protein-bound allergens by Langerhans cells (LC), resident immature dendritic cells of the skin. Following an encounter with a chemical allergen, LC become activated and subsequently migrate from the skin to the draining lymph nodes, undergoing a maturation process during the journey. Many changes have been reported to occur in LC as a result of hapten exposure including the induction of signal transduction pathways and the modulation of cell surface markers and cytokine expression. To explore further the concept of chemical allergen induced LC activation and maturation, the process has been modeled in vitro using human peripheral blood-derived dendritic cells (DC) as surrogates for LC. Microarray analysis provided a list of genes which were significantly changed, at the transcriptional level, following exposure of the DC to a model contact allergen. Subsequent analysis of a sub-set of those genes identified specific genes which appear to demonstrate good sensitivity, specificity, dynamic range, and reproducibility and thus may prove useful in the development of screening methods for skin sensitization and may also provide mechanistic information on the immune recognition phases of ACD.

2147 CYTOKINE GENE POLYMORPHISMS AND SUSCEPTIBILITY TO CHRONIC INFLAMMATORY DISEASES IN OCCUPATIONAL SETTINGS.

B. Yucesoy and M. I. Luster. *HELD/TMBB, CDC/NIOSH, Morgantown, WV.*

There is a wide range of inter-individual variation in susceptibility to occupational and environmental related diseases. Mechanisms underlying susceptibility are largely unknown, but genetic predisposition is suspected to be a major factor. Recent evidence suggests that common polymorphisms in immune/inflammatory and antioxidant genes contribute to the pathogenesis of many complex human diseases. In light of this, functional variants of these genes have been examined for evidence of association with pulmonary fibrosis in a group of ex-coal miners, accelerated decline in lung function in firefighters and irritant contact dermatitis in healthcare workers. Several significant associations appeared between cytokine gene variants and disease progress and/or severity. The tumor necrosis factor-alpha (TNFα) -308, -238 and interleukin-1 receptor antagonist (IL-1RA) +2018 variants were found associated with the development and severity of silicosis. Also, associations between accelerated decline in lung function and genetic variations in several genes which regulate inflammation were found in firefighters that can not be explained by smoking history. Specifically, the presence of IL-1 RA +2018, TNFα -238 and -308 variants were associated with the decline rate of lung function as measured by FEV_1. Individual differences in response to common irritants (sodium dodecyl sulfate, benzalkonium chloride and sodium hydroxide) were investigated in a group of healthcare workers. Initial results confirmed interindividual variability in irritant susceptibility and provided base for investigating the role of genetic variations in response to irritants. In conclusion, the data suggest that genetic variations play a role in individual variability to certain occupational diseases. Such information can be used to help identify the most susceptible populations and apply relevant information to the risk assessment process by determining safe exposure levels for the most susceptible groups of workers.

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2148 A PROSPECTIVE STUDY OF GLOBAL EXPRESSION PROFILING IN WHOLE BLOOD SAMPLES FROM INDIVIDUALS EXPOSED TO METAL FUMES.

D. Christiani[1, 5], Z. Wang[1], D. Neuberg[2], L. Su[1], J. Kim[3] and J. Chen[4]. *[1]Harvard School of Public Health, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]U.S. EPA, Research Triangle Park, NC, [4]UNC School of Public Health, Chapel Hill, NC and [5]Massachusetts General Hospital, Boston, MA.* Sponsor: R. Luebke.

Although inhalation of metal particulates is a documented cause of pulmonary and airway inflammation, an exploratory study of microarray analyses in whole blood total RNA sampled before and after occupational welding-fume exposure supported the existence of systemic responses following inhalation of metal particulate. To evaluate the duration of particulate-induced gene expression changes, we conducted a follow-up study using a similar population one year after the original study. We recruited 15 individuals with welding fume exposure and 7 non-exposed individuals. Twelve of the 22 individuals (8 in exposed group and 4 in non-exposed group) also were monitored in our previous study. Whole blood total RNA corresponding to three time points, including baseline, immediately after ~6 h of exposure, and 24 h after baseline, was analyzed using cDNA microarray technology. Similar to our previous observations, exposure-induced expression alterations in non-smoking individuals were found in genes clustered in several Gene Ontology Biological Processes, related to Immune Response and Programmed Cell Death. The small number of genes with changed expression 24 hours after baseline compared to baseline suggest that acute particulate-induced effects were transient. Comparison of paired *t* statistic distributions indicate more global changes of gene expression in the previous study, which had significantly higher level of exposure. Although smoking was a confounding factor, a dose-response pattern of global expression was evident in smokers with higher level exposure in the previous study, in contrast to almost no changes in smokers with lower level of exposure in this study. Taken together, our results demonstrated the importance of applying a paired-sample study design in population studies that generate high dimensional data and an expected high degree of inter-personal variations.

2149 ENVIRONMENTAL EXPOSURES, IMMUNE FUNCTION, AND HOST VULNERABILITY.

J. Hollingsworth. *Duke University, Durham, NC.* Sponsor: D. Germolec.

The severity of airways disease can result from a complex interaction between host genetic vulnerability and environmental exposures. Studies in humans and mice indicate that both the biologic response to inhaled toxins and immunologic function are dependent on genetic background. This presentation will focus on the mechanisms through which common environmental exposures, such as ambient ozone (O_3), can modify both innate and adaptive immune function, and the role of host genotype in determining the severity of effects. The biological response to inhaled O_3 includes: recruitment of inflammatory cells, enhanced airway hyperreactivity, perturbations in alveolar macrophage function, and alterations in the production of pro-inflammatory mediators. Exposure to ambient O_3 can enhance or suppress allergic inflammation depending on the dose and timing of exposure, indicating that inhaled O_3 can modify adaptive immune function. We recently observed that innate immunity was modified in mice exposed to O_3 and subsequently challenged

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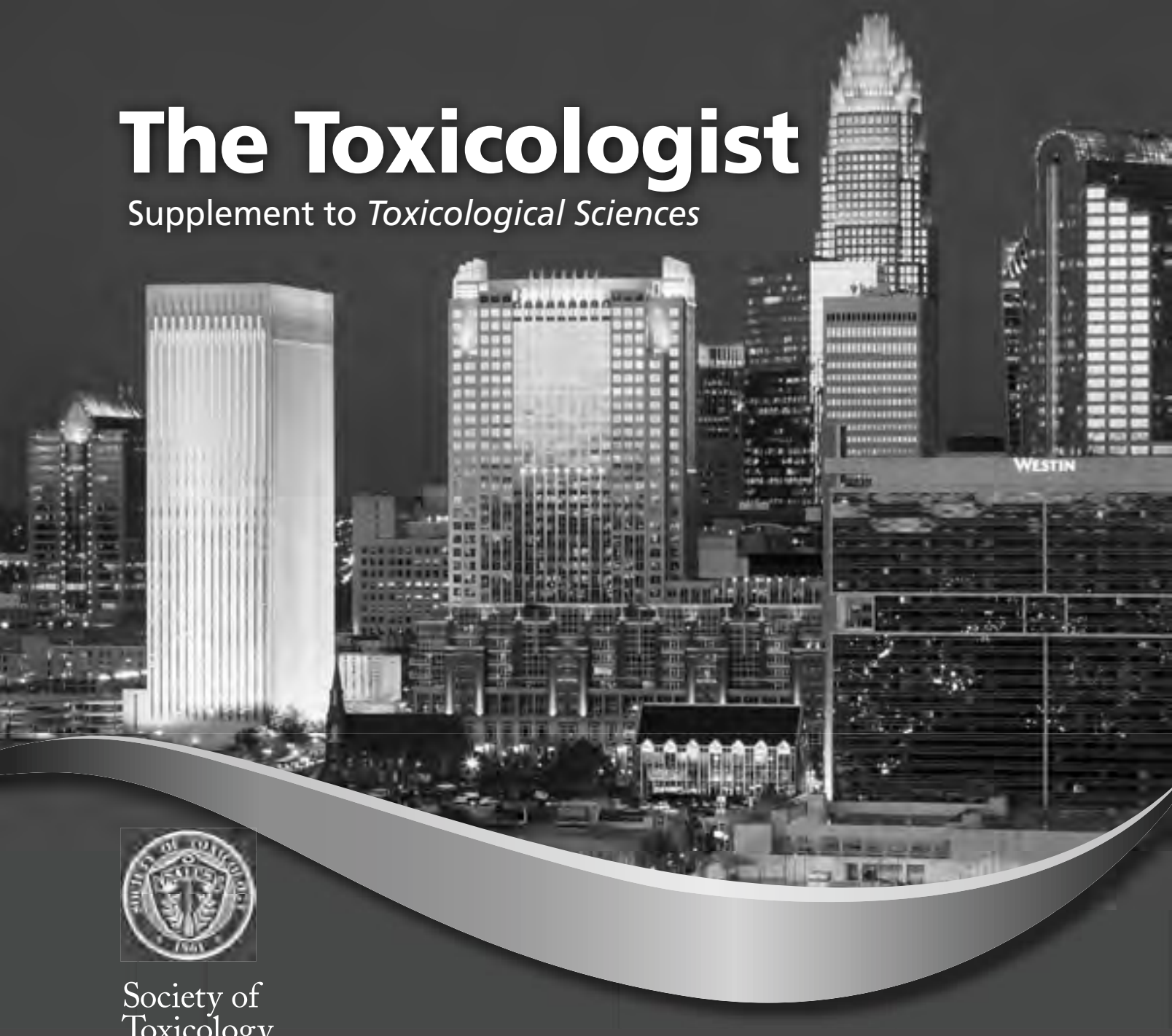

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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