sentation was contrasted on a per-site basis using an empirical Bayes method. A list of putative AhR binding sites was generated using a P1(t) cut-off to identify regions containing a high density of significantly enriched probes. Further analysis identified a number of classical DRE populated genes known to be TCDD responsive, including Cyp1b1, Aldh3a1, and Nqo1. Functional annotation identified categories known to be regulated by TCDD, including xenobiotic metabolism, mitochondrial activity and cellular proliferation, in corroboration with published reports. A few genes known to be directly activated by AhR, most notably Cyp1a1, were conspicuously absent which could be attributed to technical limitations in the promoter array or of the assay. Integration of this data with cDNA gene expression profiling allowed for the identification of putative primary gene expression responses to TCDD exposure. Overall, this study has identified novel DREs that warrant further investigation and significantly expanded the AhR gene battery facilitating further elucidation of the AhR regulatory networks. *NIH R01 ES12245 and T32 ES07255.*

783 A NEW ROLE FOR THE ARYL HYDROCARBON RECEPTOR IN REGULATING GENE EXPRESSION

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The aryl hydrocarbon receptor (AHR) is a primary participant in the molecular defense against environmental toxicants. The AHR, in addition to its role in xenobiotic metabolism, plays vital developmental roles in vascular patterning, organ modeling, extracellular matrix deposition, cell proliferation, apoptosis, and the development of the heart and immune system. We have shown by global RNA expression analysis using microarrays that the AHR appears to influence the steady-state mRNA levels of hundreds of genes. However, it is unknown at which level(s) mRNA expression is affected by the AHR, i.e., the level of transcription, nuclear hnRNA processing, or mRNA turnover. We have examined the different levels of mRNA expression regulated by the AHR by high-throughput methods using microarrays. We show that a major means by which the AHR affects steady-state mRNA levels is by regulating the processing of primary RNA transcripts in the nucleus. We conclude that although the AHR regulates key xenobiotic metabolizing genes at the transcriptional level, a larger impact of the AHR may be at post-transcriptional levels.

784 VALIDATION OF PUTATIVE BIOMARKERS FOR THE EARLY PREDICTION OF NON-GENOTOXIC HEPATOCARCINOGENESIS AND COMPARISON TO DRUG SIGNATURES

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Identifying the hepatocarcinogenicity of drug candidates requires resource-intensive 2 year chronic administration bioassays in rodents. Numerous biomarkers and mouse models have been proposed to facilitate early prediction of hepatocarcinogenicity in rodents, however, their validity is not well characterized, and it is likely that multiple gene models will be required to predict such a complex phenotype. The objective of this study was to use gene expression data from a comprehensive toxicogenomic database (DrugMatrix®), representing hepatic expression profiles of over 350 compounds, including over 100 compounds of known hepatocarcinogenic potential, in order to identify and validate putative single gene biomarkers of non-genotoxic hepatocarcinogenesis. The predictive accuracy of these biomarkers was compared to single genes on the microarray, and to multiple gene Drug Signature derived using a supervised classification algorithm. Putative single gene biomarkers involved in cell cycle (jun, fos), glutathione metabolism (GST-P, glutathione reductase), hormone signaling (androgen receptor) and many others were found to have very poor sensitivity (e.g., true positive rate). Two markers, TSC-22 and alpha2-macroglobulin, positively predicted hepatocarcinogenicity 60 and 55% of the time respectively, with specificities of 80 and 96%. Many genes with good sensitivity (>80%) suffered in specificity (<75%). By comparison, using an SPLP algorithm applied to the 100+ compound training set, we were able to derive a 45 gene signature based on day 5 liver expression data. This gene signature predicts non-genotoxic hepatocarcinogenicity with estimated performance, based on leave-one-out cross-validation, of 80% sensitivity, and 98% specificity. Genes in this signature include alpha2-macroglobulin, pyruvate dehydrogenase kinase, alcohol dehydrogenase 4, and several ESTs. Validation using other hepatocarcinogens and non-carcinogens will lead to an accurate performance estimate and determine the general applicability of this Signature

785 MONITORING CHOLINESTERASES: AN EXAMPLE OF TRANSLATIONAL RESEARCH

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Recently, the phrase "translational research" has been used to refer to projects that carry fundamental studies from the bench to clinical application. One of these arenas is the dangers posed by the modern age of pesticides and chemical warfare that require rapid, reliable, one size fits all biomonitoring. Such biomarkers include blood cholinesterases (ChEs) used to detect exposures to organophosphates and carbamates. California and Washington currently monitor pesticide and the DOD monitors chemical warfare agent handlers. Elsewhere, ChEs are determined if exposures are suspected. Surprisingly, there are few efforts to form a common database to assist public health agencies to make rapid decisions in emergency situations. This presentation reviews a decade of research translating the results of colorimeteric and pH ChE bench assays into a convertible format and to provide rapidly accessible blood ChE data to decide if dangerous exposures have occurred. Problems encountered in standardizing the assays, converting from one assay to another and the reliability of clinical laboratories are discussed and recommendations made for establishing a national data base. (Supported in part by NIOSH, DOD, NIH)

786 IDENTIFICATION OF BIOMARKERS FOR EXPOSURE OF FATHEAD MINNOW TO 2,4-DINITROTOLUENE USING CDNA MICROARRAYS - CORRELATION WITH CLINICAL SYMPTOMS IN MAMMALS

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The production of explosive 2,4-DNT and its use in military training activities has resulted in its release to the aquatic environment through various surface water pathways. The purpose of this study is to characterize the effects of 2,4-dinitrotoluene and the associated mechanisms of toxicity in the freshwater fish species, fathead minnow (Pimephales promelas), through the use of DNA microarray technology. We have used a fathead minnow cDNA microarray containing 5,000 anonymous ESTs made from RNA extracted from fish at different developmental stages from embryo to adult. Adult fish were exposed to four concentrations of 2,4-DNT (11, 22, 44, 88 μM respectively) for 10 days. RNA extracted from the liver of exposed fish and from unexposed control fish were converted into cDNA, labeled using Cy3 and Cy5 and hybridized to the cDNA microarrays. Statistical analysis of hybridization signals was used to identify 72 cDNAs that are affected by exposure to different concentrations of 2,4-DNT. Sequence analysis of the cDNA revealed that several apolipoprotein subunit genes as well as a fatty acid binding protein were down-regulated in the livers of exposed fish suggesting that 2,4-DNT interferes with lipid metabolism. Our results also indicate that 2,4-DNT interferes with oxygen transport in the blood as suggested by its effect on the expression of the hemoglobin alpha chain gene, two transferrin genes as well as genes coding for mitochondrial respiratory chain components. These observations correlate well with the results of a 2,4-DNT toxicity study which indicated that high doses of 2,4-DNT cause methemoglobinemia and anemia in exposed animals as well as an almost total absence of body fat. Our study on 2,4-DNT toxicity using a fathead minnow microarray platform suggests that cDNA microarrays can be useful to identify the mechanisms of toxicity and as a predictive tool for toxicity in mammals

787 CYP1A1 INDUCTION AND ARYL HYDROCARBON RECEPTOR ACTIVATION: DEATH PENALTY FOR PRECLINICAL DRUG CANDIDATE?

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Activation of the aryl hydrocarbon receptor (AhR) has been linked to numerous toxicological effects of dioxin. As a result, induction of AhR-regulated genes, such as Cyp1a1, is often interpreted as an indicator of the potential for a candidate drug to pose a serious threat to human health. Consequently the development of clinically interesting molecules that activate this pathway usually comes to a halt. To assess the concordance between induction of Cyp1a1 and AhR activation by small molecule drugs, and the relevance of AhR activation to preclinical drug safety assessment, we examined the expression of AhR-responsive genes in a toxicogenomic database containing gene expression profiles from short-term, repeat dose rat studies with over 630 compounds. 150 compounds were selected based on in vivo Cyp1a1 expression and screened for their ability to bind to and activate the AhR using in vitro reporter gene, gel-shift and ligand binding assays. The results indicated that 83 compounds that induced Cyp1a1 in vivo failed to activate AhR in vitro. Of the 184 marketed drugs that induced Cyp1a1 in at least one tissue, only 19 were identified as bona fide AhR ligands. These results demonstrate that induction of Cyp1a1 in vivo is a necessary, but not sufficient, indicator of AhR activation. Furthermore, these drugs do not produce dioxin-like toxicity in rats or evidence for chloracne or other adverse dioxin-like effects throughout years of clinical use. This should be expected given that these drugs are relatively weak, metabolically labile and induce AhR-dependent gene expression only transiently, while those AhR ligands that produce toxicity are resistant to metabolism and are persistent inducers. These results demonstrate that numerous clinically relevant drugs can activate the AhR signal transduction pathway without producing AhR-dependent toxicity, and that the ability of a chemical to activate the AhR pathway should not eliminate it from further evaluation or development into a therapeutic agent.

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

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

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