1224 DISSECTING MECHANISMS OF SKIN TOXICITY IN THE AGE OF PROTEOMICS AND GENOMICS.

J. D. Laskin. *UMDNJ, Piscataway, NJ.*

This talk will describe the results of using newer techniques coupling multidimensional protein separation and liquid chromatorgraphy/mass spectrometery to characterize the proteosome, and microarray analysis to describe the transcriptosome, in defining mechanisms of skin toxicity. The ultimate goal of these studies will be to identify genes that regulate the changes that occur in tissues during skin toxicity that are likely to offer novel targets for risk assessment and therapeutic intervention. Newer techniques coupling two dimensional gel electrophoresis, liquid chromatography/mass spectrometry and micro-array analysis have provided many important new leads to understand mechanisms of skin toxicity. Characterizing genes that regulate the changes that occur in tissues during skin toxicity are likely to offer novel targets for occupational risk assessment and therapeutic intervention.

1225 EXTRA CUTANEOUS ORGAN ENDPOINTS AND DEFINING KNOWLEDGE HIATUS (CLINICAL, CONCEPTUAL AND LABORATORY) WHOSE SOLUTIONS SHOULD LEAD TO INCREASED WORKER SAFETY.

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Occupational dermal toxicology surged forward in the half century since publication of the Schwartz Tullipan text. With increasing clinical experience and advancing bioanalytic and other laboratory technology in Europe, Asia, and the United States, we have become increasingly aware of the strength and weakness of current workplace health knowledge. This presentation will focus on current knowledge in the field of skin diseases, e.g., irritant dermatitis syndrome, photoirritation, allergic contact dermatitis, and contact urticaria syndrome. The talk will address the ability of the skin to inhibit percutaneous penetration, and the converse, failure to protect strength and weakness of the models systems for quantifying flux as related to the workplace (vitro vs. vivo, Q S A R, and recent shortcuts, Rougier System); models systems for quantifying decontamination in theory, practice, and need; extracutaneous end points (human organ effects) from clinical medicine and how they could be avoided; and an abridged bibliographic system permitting toxicologists to efficiently follow developments in this rapidly evolving science.

1226 XENOBIOTIC-ACTIVATED RECEPTORS: BIOLOGICAL FUNCTIONS AND DISEASE PREVENTION.

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Xenobiotic-activated receptors comprise several classes of structurally distinct receptor/transcription factors, which sense changes in the chemical environment of cells, mediate transcriptional responses to the chemical stimuli, and thereby control the homeostasis of cells. Overactivation or dysfunction of the receptors is often associated with altered responses to chemicals, including toxicity and disease states. The rapid advances in understanding of signal transduction and molecular mechanism of action of these receptors provide new insights into the biological functions of the receptors and their relation to disease pathogenesis. Moreover, increasing evidence reveals that many xenobiotic-activated receptors represent important targets for developing effective therapeutic and preventive strategies in disease control and prevention. The objective of this symposium is to bring together leading experts to present new advances in the concept and understanding of the biological functions of a number of receptors in relation to disease development and prevention. Topics include ligand-receptor interactions and implications for therapy/chemoprotection; receptor-mediated antioxidant/oxidative responses and relation to autoimmune regulation/embryonic development; and control of metal homeostasis.

1227 A NEW CLASS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR γ AGONISTS: 1, 1-BIS(3'-INDOLYL)-1-(P-SUBSTITUTEDPHENYL)METHANES.

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Diindolylmethane (DIM) and several ring-substituted analogs exhibit aryl hydrocarbon receptor (AhR) agonist activities and inhibit growth of breast and other cancer cell lines. Substitution of the methylene bridging carbon with various substituted phenyl groups resulted in loss of AhR-dependent activity. However, several of the resulting C-substituted DIMs containing p-substituted phenyl groups (pPhX) inhibited growth of cancer cell lines *in vitro* and carcinogen-induced rat mammary tumor growth *in vivo*. A series of 1, 1-bis(3'-indolyl)-1-(p-substitutedphenyl) methanes (DIM-pPhX) were synthesized and screened as potential ligands for receptors that bind lipophilic compounds. DIM-pPhX compounds induced a structure-dependent activation of PPARγ in MCF-7 breast and several other cancer cell lines. Analogs with p-trifluoromethy, p-cyano, p-phenyl, p-t-butyl and p-dimethylamino substituents were active (5 - 20 μM), whereas p-methyl, p-methoxyl, p-hydroxy or p-halo-substituted compounds were inactive at similar concentrations. DIM-C-pPhCF$_3$ and other active analogs and 15-deoxy-Δ12, 14-prostaglandin J2 (PGJ2) exhibited similar activities; however, in mammalian two-hybrid assay using PPARγ and coactivator constructs, DIM-C-pPhCF$_3$ but not PGJ2 induced interactions with PPARγ coactivator-1 (PGC-1). Like PGJ2, the PPARγ active compounds inhibited MCF-7 cell growth and G_0/G_1 to S phase progression, downregulated cyclin D1 and estrogen receptor α proteins, and induced apoptosis. However, the comparative mechanisms of cancer cell growth inhibition and induction of apoptosis by C-substituted DIMs, PGJ2 and other synthetic PPARγ agonists were variable and dependent on cell context.

1228 THE AH RECEPTOR:DIVERSITY IN LIGAND BINDING AND BIOLOGICAL/TOXICOLOGICAL RESPONSES.

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The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that mediates many of the biological and toxic effects of chemicals, including that of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD). The highest affinity AhR ligands include a variety of hydrophobic toxic and carcinogenic halogenated and polycyclic aromatic hydrocarbons, however, recent evidence demonstrates that the AhR can be bound and activated by a structurally diverse range of synthetic and naturally-occurring chemicals. While activation of the AhR and AhR-dependent gene expression by TCDD and other AhR ligands are known to produce a variety of toxic effects, anticarcinogenic/antiproliferative effects of AhR ligands have also been observed in rodent uterine and mammary tumors and in breast, endometrial, prostate and pancreatic cancer cell lines. Given the potential of AhR ligands as chemotherapeutic agents, we have carried out chemical screening in order to identify novel nontoxic selective AhR modulators (SAhRMs). High throughput screening assays using cell lines containing stably transfected AhR-responsive reporter genes has identified a variety of relatively potent new AhR agonists including a variety of flavones, benzoflavones, indirubins, tryptanthrins and related chemicals. The structural diversity of AhR ligands also suggests that the AhR contains a promiscuous ligand binding domain (LBD). Using a 3D homology model of the AhR LBD based on the crystal structures of homologous PAS family members that we developed we are attempting to identify and characterize the residues involved in AhR ligand binding. Structure-activity relationships of these toxic and nontoxic SAhRMs for AhR ligand binding and analysis of the binding of these diverse ligands within the modeled AhR LBD will provide insights into the mechanism of ligand-dependent activation of the AhR by toxic and nontoxic SAhRMs and can lead to the identification of new chemotherapeutic agents.

1229 NRF2, AN ANTIOXIDANT ACTIVATED CNC BZIP TRANSCRIPTION FACTOR: MECHANISM OF ACTION AND ROLE IN AUTOIMMUNE FUNCTION.

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NF-E2 related factor 2 (Nrf2) is a member of the cap n collar, basic leucine zipper family of transcription factors. Nrf2 mediates gene regulation by a range of chemicals with diverse structures. Activation of Nrf2 by phenolic and other antioxidants involves redox signaling. Induction of phase 2 drug-metabolizing enzyme NQO1, which catalyzes two electron reductions of quinone and quinoid chemicals, is used as a model for analyzing mechanism of gene transcription by Nrf2. Biochemical and genetic evidence demonstrate Nrf2 is required for three types of transcription of the gene: the basal expression, induction by antioxidants, and induction by AhR ligands, suggesting it serves as a master regulator of multiple signal transduction pathways in the transcription of target genes. Loss of Nrf2 function by targeted gene knock out increases the sensitivity of mice and cells to toxicity of oxidative chemicals. Moreover, Nrf2 null mice develop an early-onset, Lupus-like, autoimmune syndrome, characterized by appearance of anti-double strand DNA antibodies in young adulthood (as early as 2 month of age), multi-organ inflammatory lesions, enhanced proliferation of lymphoid cells, deposition of immunoglobulin complexes in glomerular membranes, and death due to rapid progressing, diffuse membranoglomerular nephritis. Taken together, these findings suggest Nrf2 plays critical roles in maintaining cellular homeostasis to oxidative toxicants and in physiological surveillance of autoimmune functions.

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Preface

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