with the highest risk. In order to answer this question it is essential to understand the mechanisms by which reactive metabolites can cause IDRs. It is likely that most are immune-mediated and two possibilities are that a reactive metabolite can act as a hapten or cause a danger signal. The fact that the same drug can cause a skin rash in one patient and liver toxicity in another suggests that there is a degree of random chance that determines whether T cells with the highest affinity are specific for a skin or liver drug-modified protein or even an unmodified protein leading to an autoimmune response. In fact, the same drug can cause two different types of toxicity in the same target organ, e.g. minocycline causes hypersensitivity liver toxicity in some patients with a relatively short time to onset while in others the liver toxicity is autoimmune in nature and occurs after a long period of treatment (>1 year). Therefore, the characteristics and presumably the mechanisms are different in different patients. It is likely that the location of reactive metabolite formation is a major determinant of the target of the IDR, but it is believed that an immune response in the liver requires immune activation outside of the liver. Therefore, reactive metabolite formation by macrophages may be important for the induction of an immune response. It has also been hypothesized that mitochondrial damage is important for induction of an immune response; therefore, reactive metabolite formation involving mitochondria may also be important. These hypotheses must be tested in order to understand which reactive metabolites are likely to cause IDRs. Supported by grants from CIHR.

S 17 BIOACTIVATION AND COVALENT BINDING APPLIED IN A DRUG RESEARCH SETTING.

R. Obach. *Pfizer Inc., Groton, CT.* Sponsor: J. Manatou.

The discovery and development of new drugs has been faced with the very difficult problem of failure of new agents due to low-incidence severe human toxicity, such as hepatotoxicity, that is observed only during large phase 3 clinical trials or after the drug has reached the marketplace. Thus, there have been large efforts to develop methods that can be applied in the early stages of drug research to avoid developing compounds that could cause this. A focus of these efforts has been metabolic bioactivation of drugs to chemically reactive intermediates, a process long associated with various toxicities, such as carcinogenicity. Application of in vitro assays to assess the potential for bioactivation of new compounds in early drug research has become common. Such assays include nucleophile trapping assays and covalent binding assessments. However, their fidelity is not great enough to be able to distinguish those compounds that will have unacceptable levels of toxicity in humans from those that will be generally regarded as safe. Our findings have suggested that covalent binding data alone do not distinguish toxic from non-toxic drugs and that the use of this type of data in decision-making needs to be done with great care.

S 18 KNOWNS AND KNOWN UNKNOWNS IN PROTEIN COVALENT BINDING AND TOXICITY.

R. P. Hanzlik. *Department of Medicinal Chemistry, University of Kansas, Lawrence, KS.*

The covalent binding (CVB) of xenobiotic metabolites to cellular proteins, first recognized in the 1940s, became firmly associated with acute cytotoxicity (and subsequent tissue/organ damage) in the 1970s. For many small molecules protein CVB correlates with cell injury, both in vivo and in isolated cells. Early studies emphasized addduct structure elucidation but target protein identification via C-14 labeling, 2D gels and mass spectrometry has recently accelerated. Unequivocal target identification requires the sequencing of adduct-bearing peptides but this is seldom achieved in in-life studies because the limits of detection are strained by proteins of low abundance, low fractional adduction and adduct heterogeneity. More commonly, when a single protein is identified in a radioactive spot it is assumed to be a covalently labeled target. Ironically, increased analytical sensitivity results in the identification of more proteins per spot, but fewer proteins that can confidently be called targets. This problem can be reduced by using protoxins that contain an isotopic signature, or that are amenable to pre-concentration by affinity capture via antibodies, streptavidin or click chemistry. Among >250 reported targets of >25 protoxins, few are common to ≥ 4 protoxins, and none appear to be an "Achilles heel" for the cell. Our overall knowledge of target proteins, and how they differ from non-target proteins, remains sparse. Global analysis of target lists has provided little insight into downstream mechanisms of toxicity, but bioinformatic pathway analysis of their interacting partner proteins reveals many to be involved in apoptosis, binding or response to unfolded proteins, and MAPK signaling. Future work should focus on 1) identifying more targets for more protoxins, 2) deeper bioinformatic analysis leading to hypothesis testing, and 3) attempts to evaluate the cytotoxicity of adducted proteins directly (in the sense of Koch's postulates) by introducing them into cells without using small molecules or bioactivating enzymes. (Supported by NIH-GM-21784).

S 18A DRUG HYPERSENSITIVITY: MOLECULAR ASPECTS FROM MOLECULE TO MAN.

K. Park. *University of Liverpool, Liverpool, United Kingdom.* Sponsor: J. Manatou.

Adverse Drug Reactions (ADRs) are a significant cause of patient morbidity and mortality. Frustratingly from a therapeutic perspective ADRs in a small number of patients can lead to the withdrawal of drug that is safe and effective in the majority of patients – and thus prohibit effective drug therapy and may even lead to withdrawal of the drug. Such reactions can have variable toxicological intensity and variable frequency which may be increased in certain diseases. Our approach is to understand ADRs from molecule to man and back again in order to inform the physician, patient, medicinal chemist with respect to safe drug design. The present mechanistic understanding of drug hypersensitivity is firmly rooted in the hapten hypothesis which is based on the observation that penicillins become covalently bound to protein, thus forming a hapten which is recognized by various elements of the Immune system. Based on this premise it has been assumed that the generation of chemically reactive metabolites may initiate an immune response in a similar fashion. To accept this hypothesis, there are a number of critical unanswered questions which must be resolved. We need to know how a drug (or metabolite) can perform critical immunological functions (hapten, antigen, immunogen, and co-stimulation) and what the basis of individual susceptibility is. To address these issues we have developed an integrated bioanalytical platform alongside well-defined cohorts of patients to determine the genetic basis of individual susceptibility using high-throughput genotyping platforms such as Sequenom and Illumina which enables mapping of pathways and genome wide associations; protein targets and sites of drug adduct formation in vitro and in vivo using mass spectrometry; and, chemical selectivity of T cells with a specific immunological phenotype and function and the involvement of intracellular metabolism in antigen presenting cell co-stimulatory signalling and the provision of specific antigenic determinants using ex vivo lymphocyte transformation tests and T cell cloning.

S 19 NEUROLOGICAL RESPONSES AFTER EXPOSURE TO INHALED METAL PARTICLES.

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Most studies examining the toxicology of inhaled metal particles have focused on responses in the target organ, the respiratory system. Less information exists regarding the effects associated with the inhalation of metals in extrapulmonary organs, specifically the central nervous system. There is increasing interest in the health effects of airborne incidental and manufactured metal nanoparticles (particles with one dimension <100 nm) in the environment and workplace. These smaller particles may translocate more easily from deposited sites in the respiratory tract to brain structures after inhalation. Mechanisms of particle translocation include uptake and transport along olfactory and sensory neurons, transcellular transport across respiratory epithelium to the circulation, and lymphatic clearance. Chemical composition, oxidation state, and solubility all may affect metal transport and biological responses to inhaled metals. Both animal and human studies have demonstrated that inhaled metals can translocate to the central nervous system, as well as, induce neurofunctional changes. Alterations in markers of neuroinflammation and cellular toxicity have been observed in specific brain regions using animal models after exposure to a variety of occupational particles and ambient air pollution. Cognitive deficits, brain abnormalities, and neurodevelopmental effects have been associated with exposure to metals in healthy children in Europe and North America. Our panel of experts from the fields of inhalation, neurological, metal, and occupational toxicology will highlight neurological findings of animal and human studies after occupational and environmental lung exposures. All aspects of the topic, such as metal chemistry, inhalation exposure of metal particles, metal translocation from the respiratory system to the central nervous system, and neurological responses, will be examined. An increase in the understanding of metal particle inhalation and neurotoxicity may allow for the development of prevention strategies to better protect susceptible populations in the workplace and environment.

S 20 OLFACTORY TRANSPORT OF INHALED PARTICLES AND METALS.

D. C. Dorman. *College of Veterinary Medicine, North Carolina State University, Raleigh, NC.*

One route by which an inhaled particle can access the brain is direct retrograde axonal delivery via olfactory or trigeminal presynaptic nerve endings located in the nasal mucosa. This presentation reviews experimental approaches to evaluate olfactory transport, specific metals and ultrafine particles known to undergo olfactory transport, transport mechanisms, and the development of relevant computational

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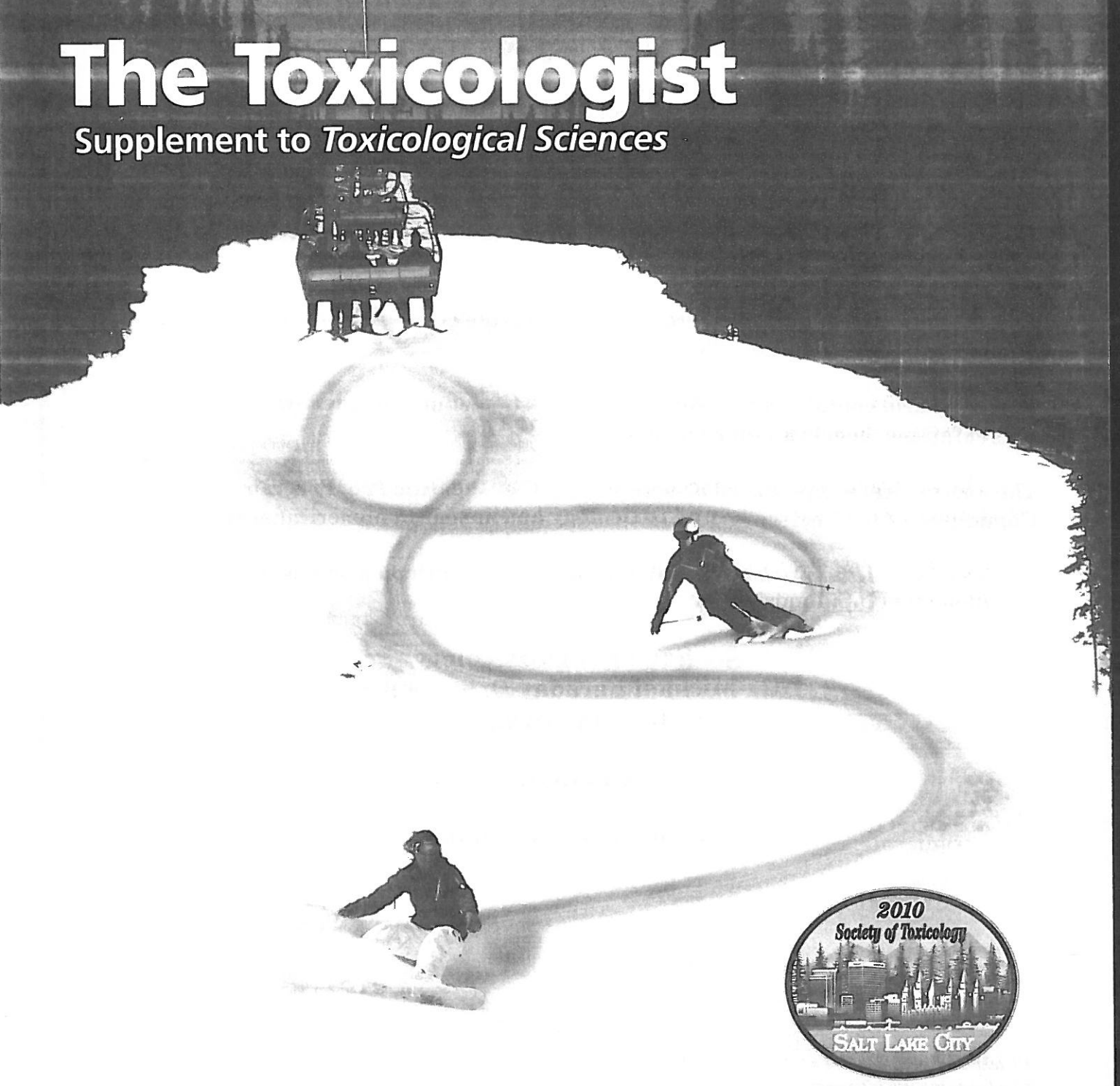

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 49th Annual Meeting of the Society of Toxicology, held at the Salt Palace Convention Center, March 7–11, 2010.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 473.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 496.

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

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