Immunotoxicology Specialty Section Newsletter

The Immunotoxicology Specialty Section Newsletter is published 3 times/year (May, August and November). If you would like to share a book review, meeting report, interesting web site or any other item of interest with members of the Specialty Section, please send it to us by the middle of the month preceding the planned publication date. All comments on, or suggestions for, the newsletter are welcome.

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President's Message

Bob Luebke

Immunotoxicology will be well represented this year at the annual meeting in New Orleans, with one CE course on Sunday and at least one morning and afternoon immunotox-related session through Wednesday. Please plan to attend the Specialty Section business meeting on Monday at 6 PM (Room 214 of the Convention Center) to catch up with everyone that you get to see once a year, to applaud winners of awards and hopefully to volunteer for service on a committee.

Welcome to the new members of the Immunotoxicology Specialty Section, and thanks for joining our group. We've had a growth spurt since the 2004-2005 Directory was published, increasing our membership from 250 to 362 (as of February 10th), so there will be some new faces at the meeting this year...please make the new members feel welcome. New and long—standing members are encouraged to get involved in the Section by volunteering for a committee, particularly if you have never served on one. The time commitment in most cases is minimal, yet committee membership provides more of an opportunity to have a hand in the direction and activity of your Specialty Section. If you are new to the Specialty Section, committee membership will also give you an opportunity to get to know other members of the section. New ideas and fresh perspectives are welcome and necessary for the future of the Immunotox Section.

As you know, a number of awards are given each year for accomplishments by members, but are only given when at least 2 papers or individuals have been nominated for an award. This year the Outstanding Young Immunotoxicologist Award could not be given because there was only one nominee. I know that we have more than one outstanding member who meets the criteria for the award; if you know someone who does, please submit their name for next year. Mentors are also encouraged to work with your students and post docs on submitting their poster or platform presentation for one of the Outstanding Presentation awards. It is a great way to recognize your student for their hard work and dedication. Criteria for the various awards are available on the Immunotox Section page of the SOT web site. It only takes a short time to complete the nomination process, and your efforts could bring someone well-deserved recognition by the Specialty Section.

Special thanks and congratulations to Beatrice Seguin (now **Dr.** Seguin), who worked very hard as the Student Representative for the Specialty Section. She was unable to attend the Annual Meeting this year, and has resigned the post. Dr. Jamie DeWitt volunteered to be our Student Representative for the next two years, and will take over for Beatrice effective immediately. Students and fellows, please remember the mixer on Tuesday at Mulates…a chance to meet other students, swap tales of life as a student, and have a chance to win a copy of the latest version of Fundamental Immunology, courtesy of Burleson Research Technologies.

See you in New Orleans.

Update on NIH Study Section Restructuring and Immunotoxicology

Submitted by Steve Pruett, Secretary/Treasurer

An SOT Task Force has been studying the Study Section issue and has obtained useful data from two Surveys that were sent to SOT members during the past year. There will be an Issues Session at the SOT Meeting in New Orleans on Wednesday at noon. Please check the announcement boards on site for the location, and make every effort to attend. Even though the surveys provide evidence of problems, it seems that the Center for Scientific Review at NIH is reluctant to admit that a problem exists. An excellent turnout at this session may help send a message.

Regulatory Committee

Submitted by Ken Hastings

At the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) meeting in Yokohama, Japan, November 14 – 18, 2004, the Immunotoxicology Expert Working Group (EWG) finalized the Step 2 document "Immunotoxicology Studies for Human Pharmaceuticals". This document, designated S8, is the result of over a year of negotiations, teleconferences, and meetings (London, October 2003; Osaka, November 2003; McLean, 2004) and represents the consensus of the EWG. The document can be found at www.fda.gov/cder/guidance/6636dft.htm and public comments are encouraged. The guidance deals with nonclinical studies to support clinical trials and marketing applications for new pharmaceuticals. The central theme of the document is unintended immunosuppression and test methods which could be useful in detecting this potential adverse drug effect. The document does not deal with other immunotoxicity issues such as drug-induced hypersensitivity reactions. The reasons for this choice are (1) apparent lack on consensus between the parties to ICH on the issue of unintended immunosuppression and (2) *de facto* consensus on other issues. The EWG decided in the Yokohama meeting to propose a weight-of-evidence (WOE) approach to deciding if specific immunotoxicity testing is needed to adequately evaluate the safety of pharmaceuticals. The WOE approach relies on signals that could be observed in standard toxicity studies, as well as other causes for concern. The document makes recommendations concerning the circumstances in which immunotoxicity studies should be conducted and the types of studies that would be useful. The conclusions and recommendations made by the EWG were based on an extensive analysis of databases assembled by Japanese, European, and US regulatory authorities, as well as other available information. It is likely that the EWG will meet in Brussels in May, 2005, to consider public comments on the draft document and consider finalization of the guidance.

Financial Statement

Immunotoxicology Specialty Section
December 2004

Submitted by Steve Pruett, Secretary/Treasurer

Jul '04 - Jun '05

Ordinary Income/Expense	
Income	
Contributions	-
Dues - '05	-
Student Dues - '04	-
Grants - Food Safety	-
Grants - Mechanisms	-
Misc. Income	-
Registrat'n	-
Interest	444
Total Income	**444**
Expense	
Awards - Sections	-
Plaques	-
Ballot	-
Exec. Mtgs.	-
Miscellaneous	-
Newsletter	250
Reception	-
Steno/Clerical	-
Symposia	-
Web Development	-
Total Expense	**250**
Excess (Deficiency) of Revenue over Expenses	194
Net Assets Beginning of Year	9,139
Transfers from General Fund	-
Net Assets Beginning of Year After Transfers	9,139
NET ASSETS END OF YEAR	**9,333**

The Society of Toxicology (SOT) has been asked to forward the following announcement concerning self-application for the Science Advisory Committee on Alternative Toxicological Methods (SACATM) to it's members.

The Science Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee that advises the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), a committee composed of 15 regulatory and research federal agencies. ICCVAM promotes the development, validation, regulatory acceptance, and national and international harmonization of toxicological test methods that more accurately assess the safety or hazards of chemicals and products. A major focus of SACATM and ICCVAM is establishing new test methods for regulatory agencies that refine, reduce or replace the use of animals.

There will be 6 openings for individuals on the SACATM committee. More information on the committee and its function can be found at http://www.toxicology.org/sacatm/index.html. Individuals with an interest in animal issues can apply by submitting an appropriate CV. A selected list applicants will be submitted to the Director of NIEHS, who makes the appointments.

Send your CV, no later than March 1, 2005, to:
Dr. William Stokes ICCVAM
Executive Director NICEATM NIEHS
P.O. Box 12233, EC-17 Research
Triangle Park, NC 27709
Email: stokes@niehs.nih.gov
(919) 541-3398

Faculty Position at Michigan State University

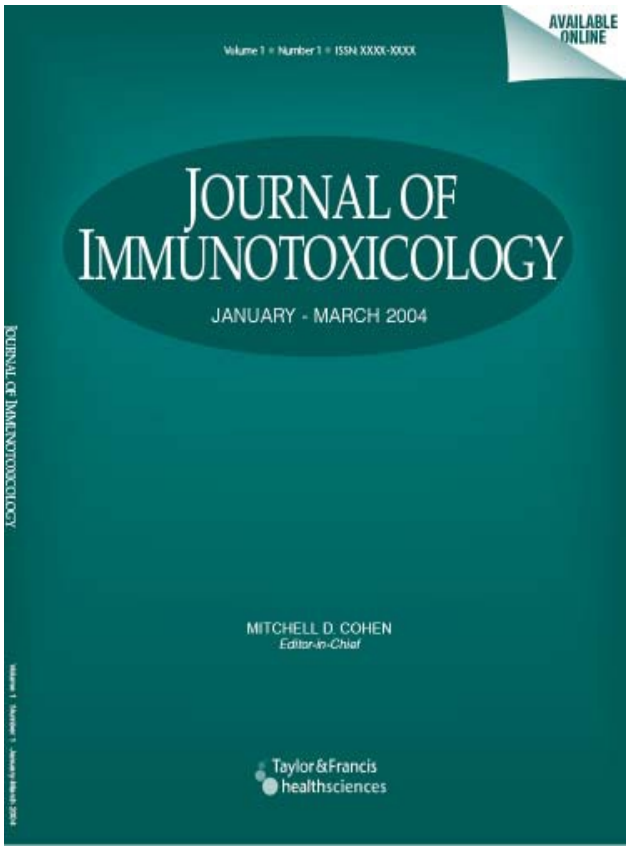
The Department of Pharmacology and Toxicology at Michigan State University is accepting applications for a tenure-track faculty position at the Assistant Professor or Associate Professor level. We are seeking candidates with an interest and expertise in inflammation as it relates to pathophysiological mechanisms or adverse consequences of drugs or other chemicals in living systems. Preference will be given to candidates who complement existing strengths in the areas of neurodegenerative, respiratory/airway or hepatic disease. Candidates should have a Ph.D. or equivalent in Pharmacology and Toxicology or related discipline, extensive postdoctoral research experience and demonstrated success in obtaining extramural funding.

The candidate will also have the opportunity to participate in dynamic and nationally-recognized interdisciplinary research and training programs including the Center for Integrative Toxicology, the National Food Safety and Toxicology Center, the Cell and Molecular Biology Program, the Center for Biological Modeling, the Genetics Program and the Neuroscience Program. The successful candidate will be expected to establish an independent and extramurally-funded research program and to contribute to teaching and other departmental activities.

Interested individuals should send their curriculum vitae, statement of research interests and future research plans, and 3 letters of recommendation to: Chair, Faculty Search Committee, Department of Pharmacology and Toxicology, Life Science B440, Michigan State University, East Lansing, MI 48824. Review of applications will begin immediately and applications will be accepted until the position is filled.

CALL FOR PAPERS

New Taylor and Francis Journal for 2004



Please submit papers to:

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Kenneth L. Hastings, Dr.P.H./DABT, Center for Drug Evaluation and Research , U.S. Food and Drug Administration

Robert V. House, PhD, Dynport Vaccine Company LLC

Robert W. Luebke, PhD, National Health and Environmental Effects Research Laboratory , U.S. Environmental Protection Agency

Jean F. Regal, PhD, Department of Pharmacology, University of Minnesota

Kazuichi Nakamura, DVM, PhD, Shionogi & Co., Ltd., Japan

Joseph G. Vos, DVM, PhD, National Institute of Public Health and the Environment (RIVM), the Netherlands

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The *Journal of Immunotoxicology* is a peer-reviewed journal that provides a needed singular forum for the international community of immunotoxicologists, immunologists, and toxicologists working in academia, government, consulting, and industry to both publish their original research and be made aware of the research findings of their colleagues in a timely manner. Research from many subdisciplines is presented in the journal, including the areas of molecular, developmental, pulmonary, regulatory, nutritional, mechanistic, wildlife, and environmental immunotoxicology, immunology, and toxicology. Original research articles as well as timely comprehensive reviews are published.

The first issue of *Journal of Immunotoxicology* appeared March 2004 and included the following articles:

"Ultraviolet Light and Resistance to Infectious Diseases" - *Annemarie Sleijffers, Johan Garssen, Joseph G. Vos, and Henk van Loveren*

"Suppression of Immune Function and Susceptibility to Infections in Humans: Association of Immune Function with Clinical Disease" - *Bob Luebke, Christine Parks, and Mike Luster*

"Immunologic Effector Mechanisms in Animal Models of Occupational Asthma" - *Jean F. Regal*

"Pulmonary Immunotoxicology of Select Metals: Aluminum, Arsenic, Cadmium, Chromium, Copper, Manganese, Nickel, Vanadium, and Zinc" - *Mitchell D. Cohen*

To Order

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IMMUNOTOXICOLOGY SESSIONS IN NEW ORLEANS

SUNDAY March 6 — 8:15 AM – 12:00 PM - CE COURSE

Immunology for Toxicologists ***(AM05 Basic)***

Chairpersons: Ian Kimber, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, United Kingdom and Dori R. Germolec, National Institute for Environmental Health Sciences, Research Triangle Park, NC.

The adaptive immune system that is found in mammals comprises a dedicated interacting system of tissues, cells and molecules that work in concert to provide specific immune responses and host resistance to pathogenic microorganisms and transformed cells. Specific immunity is supplemented by, and works in harmony with, the phylogenetically more ancient innate immune system. Immunotoxicology describes the study of adverse health effects that may result from the interaction of xenobiotics with one or more components of the immune system. Such health effects may take a variety of forms. These include frank immunotoxicity where there is functional impairment of the immune system. The concern here is that compromised immune function may translate into an increased susceptibility to infectious and/or malignant disease. A second potential consequence of the interaction of chemicals or proteins with the immune system is allergy; defined as the adverse health effects that may arise from the stimulation of a specific immune response. Allergic disease may take a variety of forms, those of greatest significance for toxicologists being skin sensitization and allergic contact dermatitis, allergic sensitization of the respiratory tract, food allergy and idiosynctratic allergic drug reactions. Finally, xenobiotics have been implicated in the induction or exacerbation of autoimmune reactions and autoimmune disease. This course will provide a grounding in fundamental and clinical aspects of immunology, and will describe the basic elements immunotoxicity, allergy and autoimmunity. The objective is to deliver an accessible guide to the immune system and immunotoxicology for general toxicologists.

An Introduction to Immunology: Fundamental and Clinical Aspects. Ian Kimber, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK.

Elementary Immunotoxicology. Robert House, DynPort Vaccine Company, Frederick, MD.

Allergy and Allergic Disease. MaryJane Selgrade, USEPA, Research Triangle Park, NC.

Autoimmunity and Autoimmune Disease. Dori R. Germolec, National Institute for Environmental Health Sciences, Research Triangle Park, NC.

MONDAY March 7 9:30 AM – 12:00 PM - SYMPOSIUM

Inhalation Exposure and Systemic Immunotoxicity: Mechanisms Linking the Lung and Immune System

Chairpersons: MaryJane Selgrade, USEPA, Research Triangle Park, NC and Judy Zelikoff, NYU School of Medicine, Tuxedo, NY.

Although toxicity to the lung and cardiovascular system are the most frequently studied targets following inhalation exposure, suppression of systemic immune responses has been observed following exposure to a number of diverse compounds. Defects in a variety of immune effector mechanisms have been observed. Frequently, these effects are not a direct result of exposure of immune targets to the chemical or its metabolites, but involve instead the production of mediators in the lung that circulate widely and/or interactions with the nervous system. Often these exposures are to complex mixtures and the active components as well as pharmacokinetics are uncertain. Many of these issues have been considered in recent studies of JP-9 jet fuel, Sarin, tobacco smoke, and different gasoline formulations, all of which suppress systemic immune responses and have the potential to impact susceptibility to infectious disease and tumor challenge in rodents. These studies have implications for public health, homeland security, industrial hygiene, and indoor environments. This symposium is a sequel to a 2004 symposium "Modulation of Host Defenses by Ambient and Source Particulate Air Pollutants" which focused on pulmonary immune response and infections.

Immunotoxicity of Aerosolized JP-8 Jet Fuel Exposure and Its Prevention by Substance P. David Harris, University of Arizona, Tucson, AZ.

Immunotoxicity of Sarin and Other Cholinergic Agents. Mohan Sopori, Lovelace Respiratory Research Institute, Albuquerque, NM.

Prenatal Exposure of Mice to Cigarette Smoke Alters Tumor Surveillance Mechanisms in the Juvenile and Adult Offspring. Judy Zelikoff, NYU, Tuxedo, NY.

Comparative Inhalation Immunotoxicity of Gasoline and Gasoline Plus Oxygenate Additives in Rats. Lorraine Twerdok, American Petroleum Institute, Washington, DC.

The Multi-Site Ambient Particle Study (MAPS): An Integrated Approach to Studying Health Effects of PM Components

Chairpersons: Robert Devlin, USEPA, RTP, NC and Terry Gordon, NYU, Tuxedo, NY.

The World Health Organization estimates that particulate air pollution (PM) is responsible for more than 500,000 deaths worldwide each year. A large number of epidemiology studies have associated PM mass with increased mortality, and the EPA currently regulates PM on the basis of mass in different size ranges. However, recent studies suggest that PM derived from different sources may differ in toxicity and that specific PM components may serve as markers for different sources, suggesting an alternative, more efficient way of regulating PM. The overall objective of MAPS was to collect particles from several different geographical regions, characterize their physical and chemical properties, and make them available to investigators for in vitro and animal instillation health studies that can relate health effects with PM components and ultimately sources. Airborne particles in the ultrafine, fine, and coarse size ranges were collected in eight different locations in the U.S. and Europe. The sites were selected to take advantage of regional differences in PM sources and components. Weekly samples were collected for a period of a month in each location, using a 3-stage particle impactor (developed at Harvard University) that is capable of collecting several mg of material during a weekly sampling interval. The particles were then assayed for a number of chemical components and made available to investigators in several different labora-tories. This symposium will describe some of the studies which have characterized health effects associated with PM and PM components from each of the different geographical locations. Relating adverse health effects to specific PM size modes and specific PM chemical components is the first step towards relating these effects to PM derived from specific sources. This will ultimately allow the EPA to more effective implement PM standards, thereby reducing no only the health impacts now associated with PM, but also their substantial impacts on quality of life and the national economy.

Sample Characterization and Source Apportionment of Ambient Particulate Matter: Combining Atmospheric Science and Lung Toxicology. John Veranth, University of Utah, Salt Lake City, UT.

Effects of Ambient PM on Oxidative Stress and Signaling Pathways. Lung-chi Chen, NYU, Tuxedo, NY.

Effects on Cytokine Production by Macrophages, Endothelium, and Epithelial Cells. Jacob Finkelstein, University of Rochester, Rochester, NY.

Health Effects of Particles from Traffic-Related Ambient Air Pollution on Respira-tory Allergy and Inflammation: A European Multisite Study. Flemming Cassee, National Institute of Public Health and the Environment, Bilthoven, the Netherlands.

Comparative Toxicity of Size-Fractionated Ambient PM Samples in the Mouse Lung. M. Ian Gilmour, USEPA, Research Triangle Park, NC.

Altered Iron Homeostasis (AIH) as a Basis for Pulmonary Immunotoxicologic Effects of Particulate Matter

Chairperson(s): Mitch Cohen, NYU School of Medicine, Tuxedo, NY and Andrew Ghio, US EPA, Chapel Hill, NC

The scientific literature is replete with reports on the pulmonary toxicologic and immunotoxicologic effects of particulate matter (PM). Although it has become increasingly accepted that the composition of PM is a major factor influencing biological effects, mechanisms to describe how composition might induce observed toxicities are mostly lacking. The altered iron homeostasis (AIH) theory postulates that specific components in PM induce alterations in the levels of free catalytically-active iron within the lungs as well as in iron availability to both lung epithelial and immune cells. These changes, in turn, impact upon local responses to infectious agents and allergens, as well as upon the release of cell products that might contribute to cardiopulmonary changes. The AIH theory not only provides a basis to explain how select PM constituents might induce these effects, but also how day-to-day or regional differences in the amounts of these components (relative to that of iron) may underlie the variability in reported health effects induced with equivalent doses of differing PM samples. Following introductory talks about the role of iron homeostasis in maintenance of immune cell functions and how components of PM may be selectively mobilized, this symposium will highlight specifically how AIH could be the basis for the observed alterations in allergic, immunologic, and cardiopulmonary responses after host exposures to PM.

The Role of Iron (Fe) Homeostasis in Immune Cell Functionality. Christopher Bowlus, University of California Davis Medical Center, Sacramento, CA

Mobilization of Metals from Particles: Immunotoxicologic Implications. Ann Aust, Utah State University, Logan, UT

Metals, Particles, and Impact Upon Pulmonary Allergic Responses. Ian Gilmour, US EPA, Research Triangle Park, NC

Effects of Particles on Fe Transport and the Immunotoxicologic Outcomes. Andrew Ghio, US EPA, Chapel Hill, NC

Do Altered Fe Status-Induced Effects on Transcription Factors Have a Role in PM-Induced Pulmonary and/or Cardiovascular Diseases? Konstantin Salnikow, National Cancer Institute, Frederick, MD

TUESDAY March 8 — 1:30 PM – 4:30 PM - SYMPOSIUM

The AhR in Cell Growth and Death

Chairperson(s): David Sherr, Boston Univeristy School of Public Health, Boston, MA and Prakash Nagarkatti, Virginia Commonwealth University, Richmond, VA.

Since its first description as a dioxin-binding protein in the 1980s, the aryl hydrocarbon receptor (AhR) has been studied primarily for its control of biologic responses to environmental agonists. However, in the last few years it has become apparent that the AhR, which clearly did not evolve to recognize environmental pollutants, likely plays an important physiologic function. Indeed, the ability of the AhR to directly regulate important cellular genes and factors such as Bax, the estrogen receptor, Rb, and NF-kB hints at a critical role for the AhR in cell growth and death. The presence of constitutively active AhR in cells that exhibit aberrant growth and apoptosis regulation, i.e., neoplastic cells, further supports this hypothesis. In this symposium, we will present several examples of AhR-mediated control of cell growth and death and will begin to detail the molecular mechanisms through which this control is manifest. In some studies presented herein, AhR function is revealed with exogenous agonists such as TCDD or PAH. In other cases, constitutive AhR function is demonstrated by modulation of AhR expression and activity in the absence of exogenous ligands. In all cases, the roles that the AhR may play in normal cellular physiology and the consequences of disruption these functions with environmental agonists are discussed.

Ligation of AhR Leads to Up-regulation of Apoptotic Genes Through DRE-Dependent and –Independent Pathways Involving NF-kB and Consequent Induction of Apoptosis in Thymocytes. Prakash Nagarkatti, Virginia Commonwealth University, Richmond, VA.

AhR Control of B-Lymphocyte Growth and Death. David Sherr, Boston Univeristy School of Public Health, Boston, MA.

Regulation of Mammary Tumor Growth Through the Aryl Hydrocarbon Receptor. Stephan Safe, Texam A&M, College Station, TX.

Current Insights into AhR-Mediated Cell Cycle Control. Cornelius Elferink, University of Texas Medical Branch, Galveston, TX.

Induction of the Intrinsic Apoptotic Pathway by Lysosomal Disruption: Influence of the Ahr. John Reiners, Wayne State University, Detroit, MI.

MONDAY March 7 — 9:30 AM – 12:00 PM - WORKSHOP

Role of Nutrigenomics in Safety Assessment of Functional Foods

Chairpersons: Madhu Soni, Burdock Group, Vero Beach, FL and Tim Zacharewski, Michigan State University, Lansing, MI.

The recent completion of human genome (blueprint) has triggered an explosion in research into how drugs might be individualized to capitalize on each patient's unique genetic code. The line between food and drug is blurring in the era of the genome. It appears that the food industry is on the verge of a new era where companies will design foods and market them to consumers according to the consumer's genetic makeup. Increased use of bioactive ingredients (so-called functional foods) is challenging toxicologists when making safety determinations. This evaluation is different from that of drugs or toxins as efficacy or benefit analysis of the ingredients has not been factored in the safety determination. The evaluation of absorption, body distribution, and metabolism will result in a realistic assessment of ranges in target tissue concentrations. Biological effects (both desirable and undesirable) can then be determined based upon genomic and proteomic changes, the result of which will be a bottom-up approach rather than a top-down methodology that imposes unrealistic safety factors. Thus, data from gene-nutrient interactions will open the ways for new concepts of risk-benefit evaluation. The proposed workshop will cover recent discoveries in nutrition, genomics, and proteomics, and how these developments will change currently used methodology for risk assessment of bioactive/functional foods. This workshop will focus on applied genomic technologies and their impact on nutrition, health sciences, and particularly on safety determination of functional foods. The objectives achieved will be: (1) provide examples of the impact of genotype (cardiovascular diseases, cancer susceptibility, allergy, etc.) on the response to foods and food components; (2) identify relevant biomarkers that are applicable for assessing the benefits and risks of selected foods; (3) FDA's thinking on use of microarray data in regulatory approvals; and, (4) regulatory and other challenges in determining safety of "nutriomic" foods.

Risk Assessment of Food and Food Components at (near) Physiological Concentrations. Ben van Ommen, TNO, 3700 AJ Zeist, the Netherlands.

Gene and Protein Expression Changes During Immune Responses to Food Allergens. Rebecca Dearman, Syngenta Central Toxicology Laboratory, Cheshire, UK.

Nutrigenomics and Inflammation. Ken Kornman, Interleukin Genetics, Waltham, MA.

Use of Microarray Data in Regulatory Approval. Dave Hattan, USFDA, Washington, DC.

Impact of Molecular Nutrition in the Safety Assessment of Foods: A SWOT Analysis. Peter Gillies, DuPont Nutrition and Health, Newark, DE.

WEDNESDAY March 9 — 8:30 AM – 11:30 PM - WORKSHOP

Toxicologic Evaluation of Inhaled Vaccines

Chairpersons: Matthew Reed, Lovelace Respiratory Research Institute, Albuquerque, NM and Robert House, Dynport Vaccine Company, Frederick MD.

Mucosal and systemic immunity stimulated by aerosolized vaccines have been recognized as effective pathways for preventative immunizations and therapies for pathogens and diseases ranging from flu (e.g., FluMist) to measles (World Health Organization) to asthma. Likewise, in the face of an ever-present risk of aerosol delivery of chemical and biological agents, inhaled vaccines make sense by stimulating immunity at the portal of pathogen/chemical entry. However, several toxicological hurdles exist for those challenged with developing or regulating vaccines, especially those designed for administration to the respiratory tract. General toxicological assessments, as are required for all vaccine subtypes, are necessary as well as special considerations including safety pharmacology. Adjuvant type and possible transport to the brain via the olfactory pathway are of concern as well. This symposium will bring together experts in the field of inhaled therapeutics and vaccine development, to give insight into the required and perceived toxicology of aerosolized vaccines.

Airway Drug Delivery Options for Inhaled Biologics and Vaccines. Chet Leach, Lovelace Respiratory Research Institute, Albuquerque, NM.

Immunogenicity and Safety Testing of Vaccines: A Regulatory Perspective on General Requirements and Special issues of the Respiratory Tract. Ken Hastings, USFDA, Rockville, MD.

Unique Issues Associated with Toxicology Assessment of Vaccines for Biowarfare Agents. Robert House, Dynport Vaccine Company, Frederick MD.

WHO-Sponsored Preclinical Toxicity Tests for Inhaled Measles Vaccine. Mark Papania, Atlanta, GA.

THURSDAY March 10 8:30 AM – 11:30 PM - WORKSHOP

Safety Assessment of Biological Therapeutic Products – Defining the Scientific and Regulatory Issues

Chairpersons: Andrea Weir, U.S. FDA CDER, Rockville, MD and Barbara Mounho, Amgen, Inc., Thousand Oaks, CA.

Biological therapeutic products (BTPs) are proteins derived from living organisms or produced via biotechnology means that have provided the medical community with novel, highly targeted therapies for the diagnosis and treatment of diseases in humans. An integral part of the safety evaluation of these products is toxicology studies. BTP- induced toxicities are typically limited to their pharmacological mechanism of action; therefore, toxicology studies need to be conducted in an animal model that expresses the receptor or epitope that is recognized by the product. Frequently, a non-human primate (NHP) is the relevant model. In recent years, the quality of NHPs and the availability of methods for assessing toxicity in these animals have increased. In spite of these advances, many challenges remain in the safety assessment of BTPs. For example, only a very limited toxicological assessment can be conducted if the only relevant model is a chimpanzee. In such cases, toxicologists use innovative approaches, including the development of surrogate molecules, to conduct toxicology studies. Therefore, identification of novel methods is an ongoing effort in the BTP arena. Regardless of the animal model used, the potential for animals to mount an immune response to BTPs (immunogenicity) exists. Because immunogenicity can confound interpretation of toxicology studies, it is another challenge facing toxicologists that can result in the need for innovative approaches to safety assessment. Additionally, because immunogenicity can occur in humans receiving BTPs, the development of animal models to predict this effect in humans is an area of ongoing research. The need for innovative, flexible approaches when assessing the safety of BTPs is reflected in U.S. FDA and international regulatory documents. The topics covered in this workshop will provide toxicologists with the most current information on the unique scientific properties of BTPs and with state-of-the-art approached to safety assessment of BTPs.

Differences Between Small Molecules and Biological Therapeutic Drug Products. Barbara Mounho, Amgen, Inc., Thousand Oaks, CA.

Immunogenicity – Impact on Toxicology Studies and Beyond. Dan Wierda, Eli Lilly and Company, Greenfield, IN.

The Nonhuman Primate as an Animal Model for the Safety Evaluation of Biological Therapeutic Agents. John Kapeghian, Charles River Laboratories, Inc. (Sierra Division), Sparks, NV.

Alternative Methods for the Safety Evaluation of Biological Therapeutic Products – Surrogate Antibodies. Janet Clarke, Biogen Idec, Inc., Cambridge, MA.

Safety Assessment of Biological Products – A Regulatory Perspective. Hanan Ghantous, U.S. FDA CDER, Rockville, MD.

MONDAY March 7 4:30 PM – 6:00 PM – SUNSET SESSION

Developmental Toxicology Evaluations: Issues with Including Neurotoxicology and Immunotoxicology Assessments

Chairpersons: Greg Ladiccs, DuPont Co., Haskell Laboratory, Newark DE and Leigh Ann Burns Naas, Pfizer, Inc., San Diego, CA.

Panelists: Robert Chapin, Prizer, Inc., Groton, CT

Larry Sheets, Bayer CropScience, Stillwell, KS

Michael Woolhiser, Dow Chemical Co., Midland, MI

Ken Hastings, U.S. FDA, Rockville, MD

Susan Makris, U.S. EPA, Washington, D.C.

Michael Holsapple, ILSI Health and Environmental Sciences Institute, Washington, D.C.

Evaluation of offspring following maternal exposures during gestation and lactation (i.e., reproductive/developmental toxicology [RDT]) has historically been a routine part of the safety assessment process. Recently, increased attention has focused on the effects of agricultural and industrial chemicals, as well as pharmaceuticals, on the developing nervous and immune systems of the fetus and newborn. This new focus on develop-mental neurotoxicology (DNT) and developmental immunotoxicology (DIT) is based on the premise that the developing nervous and immune systems may be qualitatively and or quantitatively more susceptible to chemical perturbation compared to the adult and studies conducted currently may be insufficient to protect the young. DNT studies have become common for agricultural chemicals, following the preparation of test guidelines from the U.S. EPA (OPPTS 870.6300, 1998) and OECD (Guideline 426, draft). With increased DNT testing and the prospect of new DIT test guidelines, with many scientific workshops, roundtables, symposia, as well as sponsored research devoted to the issues that are common to RDT, DNT, and DIT, including the consequences of high dose selection and maternal toxicity; the adequacy of pup exposure during lactation; whether a different dosing paradigm should be applied to RDT vs. DNT or DIT studies; whether DIT or DNT endpoints can be incorporated into a single RDT study for hazard identification purposes (e.g., for screening purposes, what endpoints have proven their value and should be retained). This session will provide a forum to discuss how assessment of RDT, DIT, and DNT could be integrated for hazard identification purposes and to reduce animal usage.

MONDAY March 7 9:30 AM – 12:30 PM – POSTER SESSION
Immunotoxicology – Methods and Safety Evaluation

MONDAY March 7 1:30 PM – 4:30 PM – POSTER SESSION
Respiratory Tract – Pulmonary, Cardiovascular and Immune Effects of PM

MONDAY March 7 1:30 PM – 4:30 PM – PLATFORM SESSION
Mechanisms of Immunotoxicity

TUESDAY March 8 9:30 AM – 12:30 PM – POSTER SESSIONS
Immunomodulation
Safety Evaluation: Biotechnology Products and Vaccines

TUESDAY March 8 1:30 PM – 4:30 PM – POSTER SESSION
Hypersensitivity

WEDNESDAY March 9 1:30 PM – 4:30 PM – POSTER SESSION
Immunotoxicology – In Vitro/Mechanisms

WEDNESDAY March 9 1:30 PM – 4:30 PM – PLATFORM SESSION
Mechanisms of Hypersensitivity

Recent Immunotoxicology Publications

Compiled by Helen Ratajczak

ANYTIME you have a new publication to report, please send it to hratajcz@rdg.boehringer-ingelheim.com It will be included in the next newsletter.

ASTHMA, ALLERGY AND HYPERSENSITIVITY

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