Mountain West Society of Toxicology

2009-2010 Annual Report

Prepared by

Matthew D. Reed, PhD, DABT

President, 2010 – 2011

Table of Contents

1 Summary

The primary activities of the Mountain West Society of Toxicology (MWSOT) encompass those functions surrounding the Annual Fall meeting as well as the MWSOT reception held at the National SOT meeting. The MWSOT annual meeting has traditionally rotated among the primary "four corner" member states of Arizona, Colorado, New Mexico and Utah. The 2009 meeting was held at the Hyatt Regency Tamaya on the Santa Anna Pueblo near Albuquerque, New Mexico. The plenary topic was "Toxicology in the Development of Countermeasures for Radiation, Chemical and Biological Threat Agents." The meeting was well attended, attracting 71 registered participants from a relatively small total membership. Speakers from academia and Lovelace Respiratory Research Institute (LRRI) discussed the plenary topic while students and postdoctoral presentations and poster sessions completed the first day of the meeting. The second day was highlighted by an Industry and Career Perspectives session, a Systems Biology Special Topics session, and student poster, presentation and travel awards. MWSOT received student travel support, speaker travel support and education and outreach support for its membership with primary direction to support the annual meeting activities. These funds, good corporate and private sponsorship, and active participation (registration fees) led to a meeting with a positive dollar outcome. As part of an active student and networking outreach program, the MWSOT membership continued a relationship with the Southern California SOT chapter by holding a joint SOT reception at the annual SOT meeting held in Salt Lake City, Utah. The reception was well-attended by both chapters and continues to be an excellent venue for the MWSOT student membership to be exposed to the majority industry-based membership of the Southern California chapter. As of August 2010 the current SOT balance statement of MWSOT was $20,565.60.

2 Chapter Information

Geography: The Mountain West chapter encompasses all of Arizona, Colorado, Utah, Nevada, New Mexico, and Wyoming. It also includes Southern Idaho.

Membership: 115.

Website: http://www.toxicology.org/isot/rc/MtWsot/index.asp

Officers:

President: Matthew D. Reed,
Vice President: Donna D. Zhang,
Vice President-Elect: Cynthia Ju**,**
Secretary/Treasurer: Kevin D. Welch,
Past President: Phillip J. Moos,
Councilors: Mingyi W. Trimble, Jean C. Pfau,
Postdoctoral Representative: Robert K. Kuester,
Senior Student Representative: Gabriel A. Knudsen,
Junior Student Representative: Chad Nicholas Brocker
Chapter Makeup: Primarily university-based. Majority of membership from major universities within the primary four-corners states.

3 General Comments:

The primary activities of the Mountain West Society of Toxicology (MWSOT) encompass those functions surrounding the Annual Fall meeting as well as the MWSOT reception held at the National SOT meeting. The MWSOT annual meeting has traditionally rotated among the primary "four corner" member states of Arizona, Colorado, New Mexico and Utah. This extensive geography and the rural nature of the intermountain west limit the primarily academic membership and increase the hardship of member travel to and from the regional chapter meeting each year. Participation at the regional meeting as well as at the national level continues to be good however. The focus of the MWSOT regional meeting has always been on student participation and student presentations.

4 Annual Regional Meeting – 2009:

The summary program of the 2009 meeting is included in Appendix A. The program contains the general schedule of events, major sponsors, guest speakers, sponsored speakers, student speakers, student posters and associated abstracts. The 2009 meeting was held at the Hyatt Regency Tamaya on the Santa Anna Pueblo near Albuquerque, New Mexico. The plenary topic was "Toxicology in the Development of Countermeasures for Radiation, Chemical and Biological Threat Agents." The meeting was well attended, attracting 71 registered participants. The meeting was fiscally viable turning a slight profit for the chapter.

Speakers from academia and Lovelace Respiratory Research Institute (LRRI) discussed the plenary topic while students and postdoctoral presentations and poster sessions completed the first day of the meeting. Day 1 started with housekeeping information from Drs. Reed (Vice President and meeting organizer) and Moos (President). Dr. Reed gave a brief discussion of the US government's approach to the development of countermeasures for chemical, biological, radiological and nuclear threats. Subsequently, the keynote discussion was delivered by Lance L. Simpson, PhD of the Jefferson Medical College. The topic was "The Life History of a Botulinum Toxin Molecule." Even for the relatively early starting time the presentation was well attended, very well received and generated a good bit of discussion. Dr. Simpson's key discussion points are included in Appendix A meeting program.

Ray Guilmette, PhD, FHPS, CRadP covered the nuclear and radiological threat agent development of generalized decorporating elements following Dr. Gary Grotendorst and Dr. Mohan Sopori's discussion of two different classes of chemical threat agents, sulfur mustard (a vesicant) and sarin gas (nerve agent). These speakers were from Lovelace Respiratory Research Institute (LRRI) in Albuquerque, NM. The abstracts of their presentations are included in Appendix A, meeting program.

Student presentations by Robyn L. Poershke, University of Utah, Ebany J. Martinez-Finley, University of New Mexico, and Alexandria Lau, University of Arizona were delivered until the early afternoon of Day 1. The toxicities of methylseleninic acid and arsenic were discussed by the speakers (Appendix A, meeting program). Student posters were judged by a volunteer panel. The remainder of the afternoon was devoted to free time.

An evening poster session and reception were held followed by the annual meeting dinner. Posters were presented by April Lake, University of Arizona, Xi Sun, University of New Mexico, Angel Leon-Buitimea, University of New Mexico, Qian Li, University of New Mexico, J. J. Galligan, University of Colorado, Karen L. Cooper, University of New Mexico, Monica Sandoval, University of New Mexico, Alexandra Fajardo, University of New Mexico, Monica Yellowhair, University of Arizona, Jason Fritz, University of Colorado, Phillip Kuehl, LRRI, Jean Pfau, Idaho State University, Scott W. Burchiel, University of New Mexico, Sheung P. Ng, LRRI, Bobby Scott, LRRI. Student posters were judged by a volunteer panel of judges.

The second day of the meeting was highlighted by an Industry and Career Perspectives session, a Systems Biology Special Topics session, and student poster, presentation and travel awards. The Career Perspectives session was designed to give students some insights into careers outside of academia. Representatives for contract research, large pharma, and small pharma gave presentations on life in each of these areas. Dr. Michael Dorato, PhD, DABT, of Covance, Dr. Kevin Kerzee, formerly of Harlan, and John W. Davis, II PhD were scheduled speakers in each respective area. Dr. Vincent Murphy, PhD, DABT stepped in for Dr. Ivan Rich, PhD who was not able to attend the meeting. Speakers were available to students for questions throughout the meeting.

The final scientific session focused on systems biology approached. Dr. Davis (discussed above), Dr. Phillip Moos, University of Utah, Dr. Kevin Harrod, LRRI, and Dr. Rahi Iyer, Los Alamos National Laboratories discussed system's analyses of viral pathogenesis, nanomaterials, and ionizing radiation respectively. All talks were well received.

Student awards presentations ended the second day. Award recipients included:

Student Travel:

Alexandria Lau, University of Arizona

Monica Yellowhair, University of Arizona

Jason Fritz, University of Colorado, Denver

Robyn Poerschke, University of Utah

Poster Awards:

1st - Jason Fritz;

2nd – Monica Yellowhair

Presentation Awards:

1st – Ebany Martinez-Finley, University of New Mexico;

2nd – Alexandria Lau

5 MWSOT Supporting Funds from SOT National:

MWSOT received three monetary funds/awards from SOT National in 2009. These included full monetary reimbursement for study travel to and from meetings. These funds (a maximum of $2,000) went to support the travel award recipient's travel to and from the regional meeting. MWSOT received speaker reimbursement funds from SOT to support guest speakers for the meeting (a maximum of $2,000). These funds as well as a travel award from Covance helped bring in out of region guest speakers. MWSOT also received a $2,000 educational outreach award. This fund went to support the regional meeting. Special emphasis was placed on the industry and career perspectives session. As discussed above, industry guest speakers were available throughout the meeting to answer student and trainee questions about potential careers outside of academia. A record of the request letters sent to SOT National for review are included in Appendix B.

6 Regional Chapter Reception at National Meeting – 2009:

At the 49th Annual National SOT meeting in Salt Lake City (March 7-11, 2010), Mountain West SOT held a joint meeting/reception with the Southern California SOT Regional Chapter (RC). This reception was held at Swatter's Pub in downtown Salt Lake City. We planned for approximately 100 attendees between the two RCs and we estimate that we exceeded this number with about an equal number showing from both RCs (the sign-in sheets were full but 'disappeared' before an accurate tally

could be made). The joint meeting/reception was a success and we continue to discuss new ways in which our two RC could expand our interactions with the eventual goal of having science focused joint meetings. However, at this time, we are still reviewing possibilities and have not generated concrete plans. Still, both RCs value these joint meetings/receptions at the National Meeting and we anticipate that we will continue this joint reception in the future.

7 Appendices:

Appendix A, PDF copy of MWSOT Annual meeting book

Appendix B, PDF copies of letters for award

Appendix C, PDF copy of current SOT ledger

APPENDIX A

Mountain West Society of Toxicology

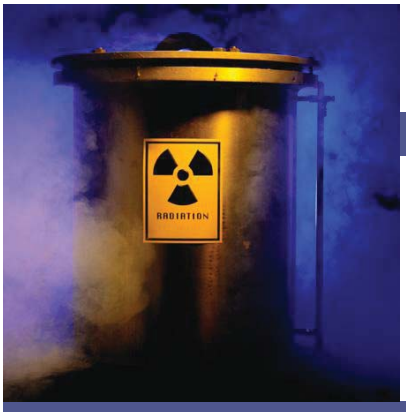
27TH Annual Regional Chapter Meeting Book




27th Annual Regional Chapter Meeting of the Mountain West Society of Toxicology

Hyatt Regency Tamaya, Santa Ana Pueblo, New Mexico

September 24 & 25, 2009



Plenary Topic:
"Toxicology in the Development of Countermeasures for Radiation, Chemical and Biological Threat Agents"

Diamond Sponsors:

Lovelace Respiratory Research Institute

Covance Laboratories

Additional funding provided by:

HemoGenix, Inc.

University of New Mexico College of Pharmacy

Mountain West Society of Toxicology

2009 - 2010

Officers:

President:	Philip Moos University of Utah (May 1, 2009 – April 30, 2010)
Vice President:	Matt Reed Lovelace Respiratory Research Institute (May 1, 2009 – April 30, 2010)
Vice President-Elect:	Donna Zhang University of Arizona (May 1, 2009 – April 30, 2010)
Treasurer/Secretary:	Kevin Welch United States Department of Agriculture (May 1, 2009 – April 30, 2011)
Councilor:	Vasilis Vasiliou (Past President) University of Colorado (May 1, 2009 – April 30, 2010)
Councilor:	Vincent Murphy Array Biopharma Inc. (May 1, 2009 – April 30, 2010)
Councilor:	Jean Pfau Idaho State University (May 1, 2007 – April 30, 2009)
Student Councilor:	Gabriel Knudsen University of Arizona (May 1, 2009 – April 30, 2011)
Student Councilor:	Michael Holt (SAC representative) University of Colorado (May 1, 2008 – April 30, 2010)
Postdoc Representative:	Robert Kuester University of Arizona (May 1, 2009 – April 30 2011)

27th Annual MWSOT Meeting
Agenda

Thursday, Sept 24 – Bear Meeting Room unless otherwise noted

7:00– 7:30 AM – Pick Up Registration Materials

7:30 – 8:00 AM - Housekeeping and Introduction
Matthew D. Reed, PhD, DABT and Philip Moos, PhD (MWSOT VP and President)

***Plenary Topic*: "Toxicology in the Development of Countermeasures for Radiation, Chemical and Biological Threat Agents"**

8:00 – 9:00 AM - Keynote Presentation
"The Life History of a Botulinum Toxin Molecule"
Lance L. Simpson, PhD
Professor Infectious Disease and Environmental Medicine
Thomas Jefferson Medical School, Philadelphia, PA

9:00 AM – Noon – Plenary Topic

9:00 – 9:30 AM
"Ricin Toxicity and Toxicokinetics Following Inhalation and Ingestion"
Janet M. Benson, PhD, DABT
Senior Scientist, Program Manager, Applied Toxicology
Lovelace Respiratory Research Institute
Albuquerque, NM

9:30 – 10:00 AM
"Scientific Basis for Developing Approaches to Decorporating Internally Deposited Radionuclides"
Raymond A. Guilmette, PhD, FHPS, CRadP
Senior Scientist, Director, Center for Countermeasures Against Radiation
Lovelace Respiratory Research Institute
Albuquerque, NM

10:00 – 10:30 AM – Coffee Break – AREA ADJACENT TO BEAR MEETING ROOM

10:30 – 11:00 AM
"Acute and Chronic Pulmonary Injury Induced by Sulfur Mustard Inhalation"
Gary R. Grotendorst, PhD
Senior Scientist, Respiratory Immunology and Asthma Program, Director CounterACT Research Center of Excellence
Lovelace Respiratory Research Institute
Albuquerque, NM

11:00 – 11:30 AM
"Neuroimmune Effects of Sarin Inhalation"
Mojan L. Sopori, PhD
Senior Scientist, Respiratory Immunology and Asthma Program
Lovelace Respiratory Research Institute
Albuquerque, NM

11:30 AM – 12:30 PM – Student Presentations

11:30 – 11:50 AM
"Effects of Thioredoxin Reductase and Methylseleninic Acid on Cell Cycle in Human Cancer Cell Lines"
Robyn L. Poerschke
University of Utah

11:50 AM – 12:10 PM
"Lower Corticosterone Receptor Levels and Deficits in Learning and Memory Behavior in C57bl/6 Adolescent Mice Following Perinatal Arsenic Exposure"
Ebany J. Martinez-Finley
University of New Mexico

12:10 – 12:30 PM
"Arsenic Induces Autophagy and Upregulates the Nrf2-Dependent Antioxidant Response Pathway through P62"
Alexandria Lau
University of Arizona

12:30 PM – MWSOT Officers Luncheon (by invitation)

1:30 – 6:00 PM – Free Time – ON YOUR OWN

5:30 – 6:00 PM – Poster Set Up – EAGLE MEETING ROOM

6:00 – 7:30 PM – Poster Session and Career Breakout Reception – EAGLE MEETING ROOM
.
8:00 – 9:00 PM – Banquet Buffet – BEAR MEETING ROOM

Friday, Sept 25th – Rio Grande Bar unless otherwise noted

7:30 – 7:35 AM – Housekeeping
Matthew D. Reed, PhD, DABT and Philip Moos, PhD (MWSOT VP and President)

***Topic II*: Industry and Career Perspectives**

7:35 – 8:15 AM
Diamond Sponsor
"The 'Discovery' Phase as a Driver for Drug 'Development': A CRO Perspective"
Michael A. Dorato, PhD, DABT
Vice President, Scientific and Technical Services
Covance Laboratories Inc.

8:15 – 8:45 AM
"Contract Research Organizations in the 21st Century: The Integration of Business and Science"
Kevin J. Kerzee, PhD, DABT
Professional Needs Assessment Task Force
Indianapolis, IN

8:45 – 9:15 AM
Sponsor
"High Throughput Stem Cell Hemotoxicity Screening and Testing"
Ivan N. Rich, PhD
Founder, Chairman & CEO
HemoGenix, Inc
Colorado Springs, CO

***Topic III*: Systems Biology and Special Topics**

9:15 – 9:45 AM
"Application of Toxicogenomics in Preclinical Safety Assessment: Evaluation of Non-Alcoholic Fatty Liver Disease Models for Investigating Drug-Induced Liver Injury"
John W. Davis II, PhD
Director, Investigative Toxicology
PGRD
Pfizer, St. Louis

9:45 – 10:15 AM
"Transcriptional Responses to Ionizing Radiation in Cells of the Skin"
Philip Moos, PhD
Assistant Professor
Department of Pharmacology and Toxicology
University of Utah

10:15 – 10:45 AM - Coffee Break – RIO GRANDE PATIO

10:45 – 11:15 AM
"Novel Mechanisms of Viral Pathogensesis Using a System-wide Approach"
Kevin Harrod, PhD
Director, Infectious Disease Research Program
Lovelace Respiratory Research Institute
Albuquerque, NM

11:15 – 11:45 AM
"Correlation of the Physicochemical Characteristics of Engineered Nanomaterials to Cellular and Tissue-level Responses"
Rashi Iyer, PhD
Technical Staff Member
Biosecurity and Public Health
Los Alamos National Labs
Los Alamos, NM

NOON – Student Awards and Concluding Remarks

ADJOURN

ABSTRACTS

THE LIFE HISTORY OF A BOTULINUM TOXIN MOLECULE: A ROADMAP FOR THE DEVELOPMENT OF MEDICAL COUNTERMEASURES

Lance L. Simpson

Department of Medicine, Jefferson Medical College, Philadelphia, PA

Botulinum toxin is a large protein that acts on cholinergic nerves to block transmitter release. Blockade of exocytosis produces muscle weakness and paralysis, including paralysis of the muscles of respiration. The extraordinary potency of the toxin, coupled with its lengthy duration of action, have made it a prime candidate as a potential bioweapon.

The processes that govern absorption, distribution, metabolism and elimination of botulinum toxin have been characterized. This was accomplished by developing high affinity antibodies that can be used as capture devices in high sensitivity immunoassays. This permitted the use of a variety of *in vitro* and *in vivo* methods to localize all steps in the life history of the toxin molecule, from its entry into the body (gut and airway absorption) until its eventual elimination from the body (hepatic transformation and excretion).

Botulinum toxin is absorbed by a specific process that involves: a.) binding to the apical surface of gut or airway epithelial cells, b.) receptor-mediated endocytosis and transcytosis, and c.) delivery of toxin to the general circulation. Absorbed toxin is distributed throughout peripheral fluid compartments, including: a.) the vaculature, and b.) the extravascular, extracellular space. The latter is the compartment that delivers toxin to cholinergic nerve endings.

Toxin that is in blood is very stable for prolonged periods of time. In addition, there is no uptake of toxin into formed blood elements, and there is only minimal binding to serum albumin. Thus, the general circulation can be viewed as a "holding compartment" for toxin that is either: a.) delivered to nerve endings to cause paralysis, or b.) metabolized and/or eliminated from the body.

The pharmacokinetic findings can be exploited to help design medical countermeasures, such as vaccines, therapeutic antibodies, and pharmacologic antagonists. Vaccine development provides a particularly good example. The fact that the toxin must be absorbed across epithelial barriers suggests that an ideal vaccine should: a.) be administered by a mucosal route, and b.) produce antibody-mediated blockade of toxin absorption into the body. The fact that the toxin has a long and stable residence time in blood suggests that an ideal vaccine should also: a.) evoke a robust circulating IgG response, and b.) produce a rapid antibody-mediated clearance from the general circulation. Finally, the fact that the toxin is delivered to cholinergic nerve endings suggests that an ideal vaccine should: a.) evoke antibodies that associate with the binding domain of the toxin, and b.) prevent toxin binding to vulnerable nerve endings. It is gratifying to report that a trivalent vaccine (serotypes A, B and E) that evokes all three of these levels of protection has been developed.

RICIN TOXICITY AND TOXICOKINETICS FOLLOWING INHALATION AND INGESTION

Janet Benson, Andrea Gomez, Molly Wolf, Edward Barr, and Thomas March

Ricin is a ribosome-inactivating protein derived from the castor bean. Because of its ease of dissemination and potential for human morbidity following exposure, the CDC has classified ricin as a Category B bioterrorist agent. Most likely routes of human exposure from a terrorist attack are inhalation and ingestion. The purposes of these studies were to: 1) Compare the acute toxicity, toxicokinetics, and histopathology of inhaled ricin in rats and mice; and 2) to compare acute toxicity, toxicokinetics and histopathology in mice following ingestion and inhalation. For the inhalation studies, 5 groups of 6 animals of both species were exposed nose only to ricin aerosols (1 um MMAD). For ingestion studies, 5 groups of 10 mice were administered ricin at 4.4 – 17.5 mg/kg by gavage. All animals were observed for up to 7 days for morbidity and mortality. Tissues were taken at necropsy for histopathological examination. Toxicokinetics was evaluated in all groups at two dose levels, chosen based on outcome of the acute toxicity studies. The medial lethal doses of inhaled ricin in rats and mice were 0.15 and 0.56 µg/kg, respectively. By comparison, the median lethal dose in mice following ingestion was 12 mg/kg. Pulmonary lesions included hemorrhage, bronchiolitis, and vasculitis. Pulmonary lesions unique to rats were edema and fibrosis. Extra pulmonary effects were noted in thymus and spleen. Target organs for toxicity following ingestion in mice included the gastrointestinal tract, liver, spleen, and pancreas, and less commonly, the kidney. Lesions persisted in animals surviving to 7 days. The clearance half time of ricin from lungs of rats and mice was less than 24 hours. Clearance of ricin from the stomach was essentially complete within 12 hours post dosing. Results confirm earlier reports that ricin is orders of magnitude more toxic by inhalation than by ingestion. We have identified species differences in the response of lungs to inhaled ricin and determined that lesions persist in animals surviving exposure by inhalation or ingestion. The long term health consequences of these lesions remain to be determined. Research conducted under NIAID contract N01-AI-40095.

PLATFORM

Janet Benson
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SCIENTIFIC BASIS FOR DEVELOPING APPROACHES TO DECORPORATING INTERNALLY DEPOSITED RADIONUCLIDES

Raymond A. Guilmette, Ph.D., FHPS, CRadP
Lovelace Respiratory Research Institute
Albuquerque, NM 87108

There is no doubt that exposure to significant amounts of radiation carries an elevated risk for adverse health effects. Exposures can results from being near an unshielded external source of radiation or from radiation due to the intake of radionuclides into the body. The latter route of exposure is difficult to assess, but also offers the opportunity to reduce radiation dose by removing the radioactive material from the body before it decays (decorporation). This talk will describe the need and approaches for decorporation, the role of dosimetry in evaluating treatment efficacy, and the impact of dose reduction on the incidence of radiation-induced disease. Finally a glimpse of current decorporation research will be given.

PLATFORM

ACUTE AND CHRONIC PULMONARY INJURY INDUCED BY SM INHALATION

Gary R. Grotendorst, Waylon Weber, Lee Blair, Mericka Lehman, Matthew Duncan, Jinkle Seagrave, Lois Herrera and Thomas March

Lovelace Respiratory Research Institute, Albuquerque, NM

Epidemiological studies of individuals exposed to Sulfur Mustard (SM) have demonstrated that the acute injury caused by SM leads to severe pulmonary disorders after a single exposure, even when the individuals did not present with acute respiratory symptoms. These investigations have indicated that exposure to SM can lead to increased incidence of asthma, airway hypersensitivity, large airway obstruction, bronchiolitis and most seriously bronchiolitis obliterans syndrome (BOS). BOS is a rare disorder that has been reported to develop in some occupational exposures most recently to diacetyl in popcorn workers. However, it is a common complication for recipients of lung transplants and ultimately leads to the failure of the transplanted lungs. In the lung transplant patients and in rodent models of lung transplant, there is strong evidence to indicate the development of antibodies against Type V collagen and an autoimmune response against this antigen are key factors leading to the transplant failure. We now have evidence that a similar molecular mechanism may be part of the underlying pathology of SM lung injury. We have developed a rat model of lung injury induced by inhalation of SM vapor. Because of the highly reactive nature of SM with biological tissues we had to use tracheal intubation to deliver the SM vapor to the lungs of anesthetized Fisher rats. SM vapor concentrations of 150 mg/m^3 were used for all studies, with exposures of 10 or 20 minutes. Control animals were intubated similarly and exposed to filtered air for 20 minutes. This model induces both acute and chronic pulmonary pathology and at the longer times after exposure, significant changes in pulmonary function, blood oxygen levels and compensating hematology. At the early time points (1-4 DPE) there is mild inflammation with some epithelial damage in the airway including necrosis and apoptosis and some epithelia sloughing. Systemically, there is a significant drop in circulating WBC's and a dose dependent damage to bone marrow progenitor cells and damage to the crypt cells in the duodenal villi. At the intermediate time points (7-14 DPE) the circulating WBC's have returned to near normal levels and the bone marrow progenitor cells have recovered. The epithelium of the airway has begun to regenerate although there are foci of subepithelial fibrotic nodules that are initiating. By 21 DPE there are more foci of fibrotic lesions with some containing lymphocytic infiltrates and a large infiltration of eosinophils into the lung parenchyma. At later time points (28-70 DPE) there is morbidity of the 20 minute exposed animals, more significant fibrosis in the lung and significant relative decreases in blood oxygen levels which are accompanied by a significant increase in hematocrit. While the molecular basis for these various responses to SM remains unclear, we feel that as in the lung transplant induced BOS, increases in the activity of matrix metalloproteinases 2 and 9 (MMP 2 and 9) are an early event that could be linked to the severe pulmonary disorders caused by SM exposure. In the lung transplant rodent models, Type V collagen a normally cryptic antigen is exposed in the airways apparently due to the activity of MMP-9. Using immunohistochemistry we have found that by 3 DPE Type V collagen has become exposed whereas little or no staining occurs in control lungs. Thus, it appears that a similar auto-immune mechanism as occurs after lung transplant may be initiated by inhalation of SM vapor. Further investigations into this model are needed to confirm this hypothesis.

PLATFORM

EFFECTS OF THIOREDOXIN REDUCTASE AND METHYLSELENINIC ACID ON CELL CYCLE IN HUMAN CANCER CELL LINES

Robyn L. Poerschke, Jerica Johnson, Philip J. Moos

Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT

Selenium is a micronutrient essential for development and may play a role in the etiology of cancer. However, the mechanisms of selenium in cancer are not well understood. One hypothesis regarding the mechanism of selenium indicates a role for the selenoprotein thioredoxin reductase 1 (TR1). TR1 is involved in cellular redox status control and functions in deoxyribonucleotide biosynthesis. As many cancers overexpress TR1, including lung and malignant melanoma, it is a potential target for cancer treatment. Also of interest is the selenocompound methylseleninic acid (MSA). MSA is a substrate of TR1 but the involvement of TR1 in the mechanism of MSA is unknown. To further elucidate the roles of TR1 in cancer and the mechanism of MSA, we utilized a lentiviral-based microRNA delivery system to knockdown TR1 expression in SK Mel 28, LOX, and A549 human cancer cell lines. NIM-DAPI cell cycle assays were then performed after 24 hr MSA treatment in cells with either microRNA control or TR1 knockdown using flow cytometry. To determine the role of TR1 in the tumorigenic phenotype of these cells, soft agar assays were performed. After 3 weeks of growth in soft agar, colonies were stained with MTT and colony growth and size was assessed. The two human melanoma cell lines, SK Mel 28 and LOX, exhibited a G_2/M phase arrest with TR1 knockdown. Interestingly, MSA also induced a G_2/M phase arrest in the SK Mel 28 and LOX cells, which differs from the G_1 arrest observed in other tumorigenic cells. This MSA-induced G_2/M phase arrest was increased in TR1 knockdown cells. Additionally, SK Mel 28 and LOX cells with TR1 knockdown demonstrated decreased colony formation, indicating a possible role of TR1 in the tumor phenotype of these cells. A549 cells showed increased G_1 population with MSA treatment but this increase was independent of TR1 knockdown. While a role for TR1 has been previously shown in soft agar growth of mouse Lewis lung carcinoma cells, no effects of TR1 knockdown on colony formation or growth were seen for A549 human lung cancer cells. Taken together, these results indicate that TR1 knockdown and MSA can induce cell cycle arrest, but the effects are cell line dependent. The soft agar assay demonstrates a potential role for TR1 in the tumorigenic phenotype of human melanoma cells, but not A549 lung cancer cells.

PLATFORM

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LOWER CORTICOSTERONE RECEPTOR LEVELS AND DEFICITS IN LEARNING AND MEMORY BEHAVIOR IN C57BL/6 ADOLESCENT MICE FOLLOWING PERINATAL ARSENIC EXPOSURE

Ebany J. Martinez-Finley[a,b] and Andrea M. Allan[a]

[a]Department of Neurosciences, University of New Mexico School of Medicine, [b]Department of Toxicology, University of New Mexico College of Pharmacy Albuquerque, NM 87131, United States

The carcinogenic potential of arsenic as a drinking water contaminant has been well studied but a few epidemiological studies suggest that arsenic can also adversely affect learning and memory in children. The corticosterone receptor (CR) receptors are an integral part of the hypothalamic-pituitary-adrenal (HPA) axis and are found throughout the central nervous system, particularly in the hippocampus, an area of the brain of central importance for learning and memory. We examined the impact of perinatal exposure to 50 parts per billion (ppb) sodium arsenate on CRs and learning and memory behavior in the C57BL6 adolescent mouse. Measurements of CRs revealed that arsenic-exposed offspring have significantly lower levels of both glucocorticoid and mineralocorticoid receptors in the nuclear subcellular fractions than controls. Exposed offspring showed longer latency to approach a novel object than controls in an object recognition task. In the 8-Way Radial Arm Maze, arsenic offspring had a significant increase in the number of entry errors on the task compared to controls. Results suggest that moderate exposures to perinatal arsenic can significantly reduce CR levels in the hippocampus and can have adverse effects on learning and memory behavior. While these studies in themselves do not provide a direct link between the learning deficits and the alterations in the HPA axis, in context with previous work on stress and learning they suggest that damage to the HPA axis by perinatal arsenic could lead to learning deficits. Overall, this data suggests that moderate levels of perinatal arsenic can have a lasting impact on offspring.

PLATFORM

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ARSENIC INDUCES AUTOPHAGY AND UPREGULATES THE NRF2-DEPENDENT ANTIOXIDANT RESPONSE PATHWAY THROUGH P62

Alexandria Lau[1], Xiao-Jun Wang[1], Fei Zhao[1], Donna D. Zhang[1]

[1]Department of Pharmacology and Toxicology, University of Arizona, Tucson, Arizona 85721, USA

Arsenic (As) is a well-known toxic and carcinogenic metal that exists in the natural environment and is present in soil, air, and well-water. Chronic, low-dose exposure of As has been associated with several different human malignancies, including skin, lung, and bladder cancers. Previously, we have shown that arsenic exposure activates the Nrf2-Keap1 antioxidant response pathway to protect against the deleterious effects of arsenic. Conversely, under basal conditions, Nrf2 is ubiquitinated by the Keap1-Cul3-E3 ubiquitin ligase complex and targeted to the 26S proteasome for degradation. In this study, we show that As induces autophagy, a "self-eating" bulk lysosomal-degradation pathway. In an As-induced autophagy model, we demonstrate the importance of p62, a critical player of autophagy, in activating the Nrf2-Keap1 antioxidant response under stressed conditions. Upon As exposure, autophagy is induced leading to upregulation of p62, which sequesters Keap1, a negative regulator of Nrf2, into autophagosomes allowing Nrf2 to translocate to the nucleus and activate the antioxidant response. The physiological role of Nrf2 activation in response to autophagy is currently under investigation.

PLATFORM

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THE "DISCOVERY" PHASE AS A DRIVER FOR DRUG "DEVELOPMENT": A CRO PERSPECTIVE

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The changes in the drug discovery/development process have been driven, according to many reviewers, by the lagging productivity in the face of drastically increased (and increasing) cost of drug development. The Tufts CSDD has published data indicating that R&D expenditures have changed from approximately $0.5 billion/drug in ~1990 to approximately $2 billion/drug in ~2005. This along with the need to solve many simultaneous equations in the drug development effort has caused pharmaceutical companies to actually look for ways to shorten cycle times, decrease overall expenditures and certainly avoid Phase III clinical drug failures. While it is common knowledge in drug development that making "no-go" decisions prior to Phase I would provide an advantage, moving safety evaluations earlier in the drug discovery phase is also an "accepted" response to making critical decisions earlier. The focus of shifting decisions to the discovery phase is not essentially to reduce or eliminate attrition, but to shift attention to an earlier, "less expensive" phase of development. This presentation will: address ways in which pharmaceutical companies can use, and effectively interact with, services supplied by CROs; discuss some of the advanced technology and how it could be used; discuss options in changing the CRO-Pharmaceutical Company interactions from transactional to strategic.

PLATFORM

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CONTRACT RESEARCH ORGANIZATIONS IN THE 21ST CENTURY: THE INTEGRATION OF BUSINESS AND SCIENCE

J. Kevin Kerzee, PhD, DABT

The concept that contract research organizations (CROs) are second tier research facilities with "pre-pharma" scientist serving as the recruiting grounds for pharmaceutical companies is a thing of the past. In today's environment, CROs are almost universally recognized as well-respected organizations with some of the top scientists, and have become true partners with biotech and pharmaceutical companies in drug development and safety. This transition occurred not only due to the ultimate understanding that CROs perform quality and timely research services, but that they are also more cost effective in achieving equivocal results as in-house pharmaceutical research operations. Furthermore, the ongoing trend of cost reductions in drug development and safety is maturing rapidly. Most graduate programs in toxicology and related fields, while providing a quality education in science, have no requirements for finance or business management training. However these are necessary skills in today's job market to fully understand how decisions are being made in the industry. This presentation will address these issues and highlight the interaction between CROs and the pharmaceutical/biotech industry, as well as how this relationship will impact the state of toxicology jobs tomorrow.

APPLICATION OF TOXICOGENOMICS IN PRECLINICAL SAFETY ASSESSMENT: EVALUATION OF NON-ALCOHOLIC FATTY LIVER DISEASE MODELS FOR INVESTIGATING DRUG-INDUCED LIVER INJURY

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Investigational and discovery toxicology are extensions of the field of general toxicology, created to fulfill the growing need for generating higher throughput, integrative, and predictive toxicological information, in an effort to reduce attrition at later stages of drug development. These novel ideas have begun to be employed more frequently and it's widely anticipated that this will pave the way for future drug testing paradigms. One aspect of this paradigm is the field of toxicogenomics and recent innovations have led to increased application of this technology in preclinical safety assessment. Combining microarray data with pathway analysis is an efficient way to integrate gene expression data into studies designed to understand mechanism(s) of toxicity and advance programs through development. Global gene expression data from livers of rats fed a high fat diet indicated significant changes in pathways involved in metabolic processes. Similar results were observed with a compound that had previously been demonstrated to cause slight elevations of serum enzymes of normal rats. The activities of key enzymes in glycolysis, pentose shunt, β–oxidation of fatty acids, and the citric acid cycle were assessed in order to characterize biochemical changes in this model.

TRANSCRIPTIONAL RESPONSES TO IONIZING RADIATION IN CELLS OF THE SKIN

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When humans are exposed to external ionizing radiation, skin is always exposed. Most human exposures result either from medical procedures, routine work related exposures, or radiation accidents. Although skin is generally exposed during human exposures to ionizing radiation, there have been few examinations of the transcriptional response to irradiation of skin's fibroblasts and keratinocytes. The transcriptional response of quiescent primary fibroblasts and keratinocytes exposed to 10 cGy to 5 Gy and then collected 4 hours after treatment was examined. RNA was isolated and examined by microarray analysis for changes in the level of gene expression. Exposure to ionizing radiation altered the expression of hundreds of genes across both cell types. Changes in RNA expression could be arranged into three main categories including: 1) changes in keratinocytes but not in fibroblasts, 2) changes in fibroblasts but not in keratinocytes, and 3) changes in both. The changes in gene expression were primarily of p53 target genes. Similar radiation-induced changes were induced in telomerase-immortalized fibroblasts or keratinocytes. In separate experiments, protein was collected and western analyzed for expression of proteins observed in microarray experiments to be over expressed at the mRNA level. Both quantitative PCR and western analysis experiments validated these transcription changes. Our results are consistent with changes in the expression of p53 target genes as indicating the magnitude of cell response to ionizing radiation.

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NOVEL MECHANISMS OF VIRAL PATHOGENESIS USING A SYSTEM-WIDE APPROACH

Kevin S. Harrod, Wanli Lei, M. Juanita Martinez, Lance Price, Ray Roberts, and Richard J. Jaramillo

The role of pollutants and toxicants on susceptibility to infection is widely studied. Conversely, the role of respiratory infections in altering drug efficacy, metabolism, and pharmacokinetics is not widely appreciated. The pulmonary tract and specifically the lung epithelium highly express a number of xenobiotic metabolizing enzymes, in particular, cytochrome p450s. It is known that a number of drugs, particularly those administered by a non-oral route, are metabolized in the respiratory tract as opposed to the more canonical metabolism by the hepatic system. Using a systems biology approach, we sought to examine the cellular mechanisms altered during infection with SARS-CoV using an *in vitro* differentiated airway epithelial cell culture system. Primary normal human bronchial epithelial (NHBE) cells were grown on air-liquid interface cultures to produce a differentiated phenotype which highly resembles that of the proximal airway epithelium, the site known to harbor replicating SARS-CoV early during the course of NHBE infection. Surprisingly, human NHBE cultures maintain morphologic structure and air-liquid barrier function for several days following infection. Gene expression profiling using an exon microarray platform was able to identify multiple gene expression clusters with distinct temporal changes during the course of infection. Gene ontology clustering analysis identified expected gene categories related to external stimuli, response to infection, and interferon-mediated pathways. Unexpectedly, a number of xenobiotic metabolism pathways and their corresponding gene ontology clusters were highly significant early during the course of infection. Indeed, a number of cytochrome p450s, some with known lung-specific expression patterns, were the most highly upregulated genes during infection. Importantly, these gene ontology categories identify a putatively important role for xenobiotic metabolism pathways in differentiation of lung epithelium and host response to infection. These findings highlight the importance of understanding canonical and noncanonical mechanisms of cellular xenobiotic metabolism in differentiation and suggest metabolic pathways as a distinct target during respiratory viral infection.

PLATFORM

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CORRELATION OF THE PHSICOCHEMICAL CHARACTERISTICS OF ENGINEERED NANOMATERIALS TO CELLULAR AND TISSUE-LEVEL RESPONSES

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The intense interest in engineered nanomaterials (ENMs) is fueling a $1B industry that is expected to reach $1 trillion by 2015. This rapid pace of engineered nanomaterials development is outpacing our ability to understand their biological impact. The unique physical and chemical properties that make engineered nanomaterials potentially useful for technological applications also make their interactions with biological systems difficult to anticipate and critically important to explore. Due to the increased or modified chemical/biological activity, photoactivity and physical dispersibility of ENMs, it is not possible to directly translate what is understood about bulk materials to the nanoscale. This non-trivial problem is compounded by its multifactorial nature (geometries, surface chemistries, and reactivities) that can act singly or in unison to elicit biological responses from multiple-level bio-systems (gene, protein, cellular, tissue and microenvironment). In the past decade LANL and DOE have invested significantly in the discovery and development of new engineered nanomaterials and technologies. The presentation will cover current effort initiated by LANL to address the critical issue of health impact of ENMs. The goal of the proposed initiative is to develop a framework for the rapid and high-throughput assessment of the properties-dependent bioimpact of engineered nanomaterials. The coordinated research effort includes integration of biological, materials and computational disciplines. We will also present data pertaining to cellular toxicity of functionalized fullerenes in three different organ cell types and organ-derived tissues.

PLATFORM

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POSTERS

HEPATIC CYTOCHROME P450 ENZYME ALTERATIONS IN HUMANS WITH PROGRESSIVE STAGES OF NON-ALCOHOLIC FATTY LIVER DISEASE

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Members of the cytochrome P450 enzyme (CYPs) families CYP1, 2 and 3 are responsible for the metabolism of approximately 75% of all clinically relevant drugs. With the increased prevalence of non-alcoholic fatty liver disease (NAFLD), patients with this disease represent an emerging population at significant risk for alterations in these important drug metabolizing enzymes. The purpose of this study was to determine whether three progressive stages of human NALFD; steatosis, non-alcoholic steatohepatitis (NASH) with fatty liver and NASH no longer fatty, alter hepatic drug metabolizing CYPs. Decreasing trends in hepatic mRNA of CYP1A2, 2D6 and 2E1 were observed with NAFLD progression, while CYP2A6, 2B6 and 2C9 mRNA tended to increase. Microsomal protein expression of CYP1A2, 2C19, 2D6, 2E1 and 3A4 tended to decrease with NAFLD progression. However, CYP2A6 protein expression increased with progression. Functional activity assays revealed decreasing trends in CYP1A2 ($p=0.001$) and 2C19 ($p=0.05$) enzymatic activity with NAFLD severity, and while not significant, CYP2D6 ($p=0.062$) and 3A4 ($p=0.180$) also tended to decrease. In contrast, activity of CYP2A6 ($p = 0.001$) and CYP2C9 (diclofenac $p=0.0001$; tolbutamide $p = 0.004$) was significantly increased with NAFLD progression. Increased expression of pro-inflammatory cytokines, tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β), were implicated as factors causing decreased CYP activity. Further, elevated CYP2C9 activity with NAFLD progression was correlated to increased hypoxia identified by hypoxia induced factor 1 alpha (HIF-1α) expression and downstream target gene induction. Conclusion: Later stages of NAFLD cause significant changes in hepatic drug metabolizing CYPs. These data strongly suggest that caution should be taken when recommending standard dosing regimens of therapeutic drugs to patients with severe NAFLD.

POSTER #1

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ARSENIC RELEASES ZINC IN THE ZINC FINGER MOTIF DERIVED FROM PARP-1 BY THE REPLACEMENT OF ZINC

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Arsenite inhibits UV radiation (UVR)-induced poly(ADP-ribose) polymerase-1 (PARP-1) activation, which contributes to oxidative DNA damage. Interaction of arsenite with the PARP-1 zinc finger domain is one likely mechanism for the inhibition of PARP-1 activation. In this study we report that both arsenite and N,N,N,N′-tetrakis(2-pyridylmethyl) ethylenediamine (TPEN), an zinc chelator which leads to cellular zinc deficiency, increase UVR-induced 8-hydroxyl-2'-deoxyguanine (8-OHdG) formation in human keratinocytes. Spectroscopic study and mass spectrometry analysis reveal that arsenite can compete with zinc for the same binding site of an apopeptide representing the first zinc finger of PARP-1, suggesting it might lead to zinc release from PARP-1 in the cells. To determine if the substitution of arsenic to zinc in the PARP-1 leads to the inhibition of PARP-1 activity, we treated the HaCat cells with arsenite and TPEN, then detected PARP-1 activity in the cell extracts and measured the zinc content in the PARP-1 purified from cell extracts by immunoprecipitation. We found that low concentration of arsenite suppressed PARP-1 activity and released the zinc in the PARP-1 in the HaCaT cells. Similarly, removing zinc with TPEN treatment also decreased PARP-1 activity. Our finding demonstrates that arsenite inhibits PARP-1 activity by releasing zinc from zinc finger domain in the PARP-1, contributing to the enhancement UVR-induced oxidative DNA damage.

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POSTER #2

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POTENTIAL ROLE OF ETHANOL IN THE SIGNALING OF CELL GROWTH AND OXIDATIVE STRESS IN HUMAN MAMMARY EPITHELIAL CELLS

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Breast cancer is one of most frequent cancers in women worldwide. Alcohol consumption (ethanol, EtOH) has been associated with an increased risk of breast cancer. However, the mechanism(s) of EtOH-associated carcinogenesis is not understood. The primary metabolite of ethanol is acetaldehyde (AA), which is formed by two pathways involving alcohol dehydrogenases and CYP2E1. AA is known to be carcinogenic in animal models, largely via its binding to DNA and the formation of DNA adducts. We are interested in the CYP2E1 pathway because reactive oxygen species (ROS) are formed through this pathway. We have shown previously that ROS can activate EGFR signaling pathways leading to tumor promotion. In the present work, we investigated the effect of various *in vitro* EtOH exposures that are relevant to achievable blood concentrations in humans to determine if EtOH alters MCF-10A cell growth. Cells were cultured in serum-free media with or without EGF at 10% CO_2 and 37°C. Treatments were run in triplicate at 0, 10, 30 and 100 mM ethanol. EtOH-related growth effects were evaluated using a MTS assay. The expression of alcohol dehydrogenase (ADH1A, ADH1B and ADH1C), aldehyde dehydrogenase (ALDH2) and CYP2E1 were assessed using qRT-PCR and Western blot. Results showed that growth of MCF-10A cells for up to 7 days either with or without EGF, showed no significant effects related to EtOH exposure. MCF-10A cells expressed significant mRNA levels of ADH1B, ALDH2 and CYP2E1 and the protein expression was identified by Western blot. Current studies are aimed at characterizing these enzymes for expression in primary human mammary epithelial cells (HMEC). Our hypothesis is that the levels of CYP2E1 may correlate with the amount of ROS formed in response to EtOH exposure and that ROS may signal EGFR in HMEC. It is important to characterize the differential expression of CYP2E1 in different HMEC donors to determine whether this enzyme is responsible for the differential sensitivity of women to EtOH-induced breast cancer.

POSTER #3

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IMMUNOTOXICITY OF POLYCYCLIC AROMATIC HYDROCARBONS AND ARSENIC FOLOWING COMBINED EXPOSURES IN C57BL/6N MICE SLEEN CELLS

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Polycyclic Aromatic Hydrocarbons (PAHs) and arsenic are both environmental agents that are known to have significant immunotoxicity. Previous studies have shown that PAH exposure of spleen cells *in vitro* produces significant immune suppression of humoral immunity, especially when P450 activation products are examined. Exposure to arsenic, particularly sodium arsenite, has also been found to be suppressive to antibody responses *in vitro* and *in vivo*. The purpose of the present studies was to examine the immunotoxicity of PAHs and arsenite following co-exposures with the theory being that the agents may exert synergistic actions based on their different mechanisms of action. Spleen cells were isolated from male C57BL/6N wild-type mice and treated with PAHs and/or arsenic (arsenite or arsenate). Immunotoxicity assays were used to assess the T-dependent antibody response to sheep red blood cells (SRBC), measured by a direct plaque forming cell (PFC) assay. Cell viability was measured by trypan blue staining. Spleen cell viability was not changed following four days of PAH and/or arsenic treatment. However, the SRBC PFC response demonstrated that the IgM antibody response was suppressed by either PAHs or arsenic in a dose dependent manner. The PAHs and their metabolites investigated included benzo[a]pyrene (BaP), BaP-7,8- diol, benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE), 7,12-dimethylbenz[a]anthracene (DMBA) and DMBA-3,4-diol. Metabolites were found to be more potent than parent compounds in producing immunosuppression. Interestingly, dibenzo[a,l]pyrene (DB[a,l]P), a recently discovered potent carcinogenic PAH, was also found to be strongly immunosuppressive in our study. In addition, combination treatments of "no effect" concentrations of PAHs and arsenic resulted in significant immunosuppression. These results suggest that arsenite potentiates PAH-induced immunosuppression. The purpose of these studies will be to characterize to the mechanism of potentiation of PAH immunosuppression by arsenite, which we believe may be associated with p53 sensing of genotoxicity.

This work was support by a UNM HSC Environmental Health Signature Program (EHSP) pilot study grant.

POSTER #4

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SELECTIVE UPR SIGNALING FOLLOWING A RODENT MODEL OF CHRONIC ETHANOL INGESTION

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Chronic ethanol consumption remains the predominant cause of liver injury in the United States, affecting nearly 2 million people. Currently, the mechanisms behind the progression of alcoholic liver disease (ALD) remain to be elucidated. In the past decade, stress of the endoplasmic reticulum (ER) has been implicated in numerous disease states, most notably ALD. ER stress is broadly characterized as a build-up of unfolded or misfolded proteins within the ER, resulting in numerous signaling cascades, termed the unfolded protein response (UPR). These pathways are designed to decrease global protein translation while upregulating key enzymes responsible for antioxidant defenses, protein folding and lipid metabolism. Although studies have implicated UPR signaling following chronic ethanol consumption in rodent models, the precise pathways have yet to be unraveled. Current research is focused on the role of UPR signaling in a rodent model of chronic ethanol consumption. Stress of the ER provides a likely mechanism behind the pathological consequences associated with chronic ethanol ingestion.

POSTER #5

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IN VIVO INDUCTION OF POLY(ADP-RIBOSE)POLYMERASE-1 FOLLOWING ULTRAVIOLET RADIATION

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Skin is a target tissue for arsenic carcinogenesis. Low arsenic concentrations enhance DNA damage and skin tumors in mice following ultraviolet radiation (UVR) exposure, but, the underlying mechanisms are unclear. Inhibition of DNA repair enzymes such as Poly(ADP-ribose)polymerase (PARP-1) by arsenic are under investigation, yet little is known about PARP-1 activation by UVR in the skin. Our aim is to characterize the *in vitro* and *in vivo* kinetics and dose dependence of PARP-1 activation following UVR exposure. Skh-1 mice (hairless) were exposed to solar simulated UV irradiation (7 kJ/m^2 to 35 kJ/m^2). Skin samples were collected from unexposed mice and post exposure, then analyzed for cyclobutane pyrimidine dimers (CPDs) and 8-hydroxy-2'-deoxyguanosine (8-OHdG), products of DNA damage, and PARP-1 activity using immunohistochemistry. CPD formation and PARP-1 activation were evident at 14 kJ/m^2. At this UVR dose, CPDs were detected as early as 10 minutes and persisted up to 2 hours post exposure. PARP-1 activation was maximal at 1 hour and returned to control levels by 4 hours. These experiments reveal conditions for further studies which will focus on the interactions of arsenic and UVR *in vivo.* This work was supported by NIH award R01 ES015826.

POSTER #6

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THE EFFECTS OF ARSENITE AND ZINC ON UV-INDUCED DNA DAMAGE

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Arsenic is a naturally occurring environmental toxicant which is clear, odorless, and almost tasteless by nature. The greatest source of human exposure is from arsenic-contaminated water. We are studying inorganic arsenic, specifically arsenite or As(III), which is more toxic than arsenate, or As(V). Although arsenic affects many cellular processes, we are studying PARP-1 [Poly ADP-ribose polymerase-1], an enzyme involved in repairing DNA damage. We have shown previously that PARP-1 activity is inhibited by As(III) and As(III) can displace zinc from a zinc finger motif in the N-terminal DNA-binding domain. The zinc finger motifs are important in detecting DNA strand breaks and recruiting appropriate enzymes for DNA repair.

Recent findings have shown that arsenite inhibits PARP1 activity and increases UV-induced DNA damage, both of which are reversed by the addition of zinc. This laboratory has also shown that arsenite replaces zinc in a zinc finger of PARP-1. HPRT mutation assays show that UV-induced mutations are significantly increased in the presence of arsenite and decreased to near control levels by the addition of zinc. Zinc alone initially appeared to induce mutations; however further studies demonstrate that the addition of zinc does not increase mutation rate. Using this data, further experiments will be performed with zinc in combination with arsenite to determine whether zinc does counteract the toxic effects of arsenite in PARP-1 activity, DNA repair, and genotoxicity.

POSTER #7

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ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR BY TOCOPHERYL-QUINONE IN HUMAN PROSTATE CARCINOMA CELLS

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Tocopherylquinone (TQ) is the oxidized product of vitamin E. Our previous studies have shown that TQ has significant effects on prostate cancer cells including inhibition of cell growth, altered gene expression, and inhibition of androgen receptor activity. Here we report that TQ was found to activate the aryl hydrocarbon receptor (AhR) in prostate cancer cells, which may, in part, be responsible for TQ's activity in these cells. The AhR is a ligand induced transcription factor that is involved in xenobiotic metabolism and regulates the expression of several genes involved in Phase I and II metabolism. In this study we demonstrate TQ's inhibition of cell proliferation in prostate cancer cell lines is dose-dependent. Investigation of LNCaP prostate cancer cells treated with TQ demonstrated an increased expression of mRNA that are markers of AhR activation responsive signaling pathways. For example, upon treatment with TQ, LNCaP cells demonstrated a significant increase in CYP1A1 mRNA expression, a well-established marker of AhR activation. In addition, messenger RNA levels for aldoketoreductase 1C1, aldoketoreductase 1B10, glutamate-cysteine ligase, and NAD(P)H oxidoreductase 1 were increased. Importantly, we demonstrate a significant increase in activation of the AhR by TQ treatment using an AhR-sensitive luciferase reporter assay in LAPC4 prostate cancer cells. The AhR was recently shown to be an important mediator of the AR, acting as an adaptor for ubiquitin ligases. We propose that TQ's inhibition of AR expression may be due to the activation of the AhR. Future studies will focus on determining AhR activity and AR expression upon TQ treatment in prostate cancer cells. Results from these studies suggest that TQ activates the AhR, which may impact endocrine functions in prostate cancer cells.

POSTER #8

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DEPLETED URANIUM INDUCED DNA STRAND BREAKS IN CHINESE HAMSTER OVARY CELLS

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DNA damage has been implicated in the genotoxicity of many heavy metals. The aim of this study is to evaluate the genotoxicity of depleted uranium (DU) in Chinese Hamster Ovary cells (CHO) with varying mutations in DNA repair pathways. CHO cells were exposed to 0 – 300 μM of soluble depleted uranium as uranyl acetate (UA) for 0 – 48 hr. Intracellular DU concentrations were measured via inductively coupled mass spectrometry (ICP-MS). Cytotoxicity was assessed *in vitro* by clonogenic survival assay. DNA damage response was assessed via Fast Micromethod® to determine UA induced DNA single strand breaks. Results indicate that UA is entering the CHO cells, with the highest amounts found in the nucleus of all cell lines compared to the cytosol and total intracellular cell concentrations. Clonogenics assay shows that UA is cytotoxic in each cell line with the greatest cytotoxicity in the base excision repair deficient EM9 line and nuclear excision repair deficient UV5 cell line compared to the non-homologous end joining deficient V3.3 cell line and the parental AA8 cell line after 48 hr. This may indicate that UA is producing single strand breaks and UA-DNA adducts rather than double strand breaks in CHO cells. Fast Micromethod results indicate there are increased amount of single strand breaks in the EM9 cell line after 48 hr UA exposure compared to the V3.3 and AA8 cell lines. These results are consistent with previous studies that indicate DU induces DNA damage via strand breaks and uranium-DNA adducts in treated cells. These results suggest that: (1) DU is genotoxic in CHO cells, and (2) DU maybe inducing single strand breaks rather than double strand breaks in vitro. We are currently examining the possible formation of UA-DNA adduct formation to better understand the DNA damage stimulated by exposure to DU. This work is supported by NIH Grants CA096281 (RCL), F31ES014971 (MY), P30ES006694, P42ES004940 and The Alfred P. Sloan Foundation (MY).

POSTER #9

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MURINE ALVEOLAR MACROPHAGES DIFFERENTIALLY STIMULATE THE GROWTH OF NORMAL AND NEOPLASTIC DISTAL PULMONARY EPITHELIAL CELLS

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Rationale: Lung cancer kills more people than breast, colon and prostate cancers combined. While lung cancer is initiated due to numerous environmental and genetic factors, promotion of these initiated cells occurs in the context of chronic inflammation. Alveolar macrophages that coordinate chronic lung disease increase dramatically during chronic inflammation and tumor progression. In mouse models of human lung cancer, tumor growth is inhibited upon macrophage depletion, and exacerbated by chemically-induced inflammation. The mechanisms of macrophage-mediated lung tumorigenesis are currently under investigation.

Methods: Chemical carcinogens can induce lung tumors in mice that parallel human disease, facilitating mechanistic evaluation of lung tumor progression. Isolated bronchoalveolar lavaged (BAL) macrophages from naïve or tumor-bearing animals were co-cultured with primary Clara cells, primary tumor cell isolates, or stable non-tumorigenic and neoplastic lung epithelial cell lines to directly assess effects of macrophages on epithelial proliferation.

Results: Neoplastic lung cells grew more rapidly when co-cultured with macrophages from either naïve or tumor-bearing animals; this stimulation required activation of kinases associated with growth and survival. Conversely, proliferation of primary Clara cells from naïve mice was more potently stimulated by BAL macrophages from lung tumor-bearing animals. Soluble proteins responsible for enhanced epithelial proliferation in conditioned media from macrophage cultures were concentrated or removed by size-exclusion filters, and identified by ELISA. Growth factor identification was validated by addition of recombinant proteins and selective growth factor receptor inhibitors to epithelial cultures.

Conclusions: Mouse alveolar macrophages can directly stimulate proliferation of non-neoplastic and neoplastic epithelial cells in a time and macrophage education-dependent manner through soluble mediators. (Supported by CA33497 and CA15532; Fritz, J.M. is a American Foundation for Pharmaceutical Education Fellow.)

POSTER #10

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EFFECT OF PARTICLE SIZE ON THE REGIONAL DEPOSITION OF TECHNITIUM-99M LABELED PARTICLES IN RODENTS

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There is extensive information detailing the deposition patterns of various particles in the human respiratory tract and several manuscripts detailing deposition in preclinical species. However, the majority of the data in rodents was generated prior to significant advancements in rodent imaging capabilities. In order to address this need and determine the effect particle size has on the deposition patterns in rodent species, these experiments were conducted. Rats and mice were exposed, via nose-only inhalation, to particles ranging from 0.5 to 5 microns mass median aerodynamic diameter (MMAD). The aerosols were composed of technetium-99m radiolabeled sulfur colloid particles. Aerosols were generated with a series of compressed air jet nebulizers to achieve each desired particle size (0.5, 1.0, 3.0, and 5.0 microns). Aerosol samples were collected to characterize the activity aerosol concentration and the particle size distribution. Impactor analysis detailed that mass and activity median aerodynamic diameters (AMAD) correlated with each other. For example, for the target particle size of 0.5 micron the MMAD was 0.62 micron and the AMAD was 0.57 micron. These data indicate that the aerosols of Tech-99m and the sulfur colloid particles were homogeneous. Data analysis indicated that Increasing particle size resulted in an increase in deposition in the nasal region and stomach uptake. Smaller aerosols, especially at 0.5 micron, showed an increase in lung deposition. A 3-dimensional segmentation analysis was developed to enable further resolution on the particle deposition by region in the lung. This automated process showed that the smallest aerosols had enriched uptake in the peripheral lung, while larger aerosols had limited peripheral lung deposition.

POSTER #11

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OXIDATIVE STRESS LEVELS FOR ASBESTOS-EXPOSED MACROPHAGES ARE MAINTAINED BY THE Xc^- TRANSPORTER

Aaron Ferro, Jason Overocker, Jean Pfau

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Asbestos exposure leads to increased production of autoantibodies in both mice and humans, raising the risk of systemic autoimmune disease, but the mechanism of this immunologic effect is not clearly understood. Since there are few treatments for systemic autoimmune disease, there is a real need for a better understanding of the cells and mediators involved. Our lab is studying asbestos-induced autoimmunity at the levels of both induction and outcomes. At the level of induction, we know that asbestos causes oxidative stress on certain types of cells (i.e., macrophages). Oxidative stress can be a result of low glutathione levels inside the cells and can alter the function and viability of affected cells. We hypothesized that asbestos-induced oxidative stress would cause upregulation of a transport system called the Xc- transporter. This transporter exchanges glutamate inside the cell for cystine outside the cell. Inside the cell, cystine is reduced to cysteine, which can then be converted to glutathione. As an anti-oxidant, glutathione protects cells from the effects of oxidative stress. Using flow cytometry, we demonstrated that asbestos significantly increased expression of Xc- on macrophages, and that this upregulation was prevented when cells were provided cysteine (N-acetylcysteine). Further, we demonstrated that culturing the macrophages in the presence of excess cystine reduced asbestos-induced cell death, suggesting that the upregulated transporter was able to protect the cells by importing cystine. Finally, we blocked the Xc- transporter with 5 mM glutamate, which resulted in cell death even at very low levels of asbestos, but it was not toxic by itself. These results suggest a specific cellular/molecular effect of asbestos that may impact the ultimate immunologic outcome of exposure.

POSTER #12

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IMMUNOTOXICITY AND BIODISTRIBUTION ANALYSIS OF ARSENIC TRIOXIDE IN C57Bl/6 MICE FOLLOWING A TWO-WEEK INHALATION EXPOSURE

Scott W. Burchiel[1], Leah A. Mitchell[1,2], Fredine T. Lauer[1], Xi Sun[1], Jacob D. McDonald[3], Laurie G. Hudson[1], and Ke Jian Liu[1]

[1]The University of New Mexico College of Pharmacy, Toxicology and Pharmaceutical Sciences Program, Albuquerque, NM 87131; [2]Current address: Colorado State University, Veterinary Teaching Hospital, Fort Collins, CO 80523; [3]The Lovelace Respiratory Research Institute, Albuquerque, NM 87109

In these studies the immunotoxicity of arsenic trioxide (ATO, As_2O_3) was evaluated in mice following 14 days of inhalation exposures (nose only, 3 hrs per day) at concentrations of 50 μg/m^3 and 1 mg/m^3. A biodistribution analysis performed immediately after inhalation exposures revealed highest levels of arsenic in the kidneys, bladder, liver, and lung. Spleen cell levels were comparable to those found in the blood, with the highest concentration of arsenic detected in the spleen being 150 μg/mg tissue following the 1 mg/m^3 exposures. No spleen cell cytotoxicity was observed at either of the two exposure levels. There were no changes in spleen cell surface marker expression for B cells, T cells, macrophages, and natural killer (NK) cells. There were also no changes detected in the B cell (LPS-stimulated) and T cell (Con A-stimulated) proliferative responses of spleen cells, and no changes were found in the NK-mediated lysis of Yac-1 target cells. The primary T-dependent antibody response was, however, found to be highly susceptible to ATO suppression. Both the 50 μg/m^3 and 1 mg/m^3 exposures produced greater than 70% suppression of the humoral immune response to sheep red blood cells. Thus, the primary finding of this study is that the T-dependent humoral immune response is extremely sensitive to suppression by ATO and assessment of humoral immune responses should be considered in evaluating the health effects of arsenic containing agents.

The authors would like to thank Dr. Abduhl-Mehdi Ali in the UNM Dept of Earth and Planetary Sciences for his assistance in the analysis of arsenic by ICP/MS. These studies were supported by a supplement to NIEHS P30-012072 and by RO1 ES15826.

POSTER #13

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EFFECTS OF PRENATAL EXPOSURE TO CIGARETTE SMOKE ON T-LYMPHOCYTE-MEDIATED TUMOR SURVEILLANCE MECHANISMS DURING TUMOR DEVELOPMENT

Sheung P. Ng[a], Allen E. Silverstone[b], Zhi-Wei Lai[b], Judith T. Zelikoff[c]

[a]Lovelace Respiratory Research Institute, Albuquerque, NM; [b]SUNY Upstate Medical University, Syracuse, NY; [c]New York University School of Medicine, Tuxedo, NY

Epidemiological studies suggest that prenatal cigarette smoke (CS) exposure increases the incidence of some childhood cancers. A previous study in this laboratory has demonstrated that male mice exposed prenatally to mainstream CS had a higher incidence of transplanted tumors and reduced cytotoxic T-lymphocyte (CTL) activity. In the current study, mouse dams were exposed to mainstream CS (4 hr/d, 5 d/wk) or air during gestation at a particle concentration of 15 mg/m^3. Their male offspring (at 5 wk of age) were then subcutaneously injected with EL4 lymphoma cells. The results demonstrated that splenocyte CTL activity against EL4 cells was significantly suppressed by prenatal CS exposure at 8 and 15 d after tumor cell injection; $CD8^+$ (CTL) cells isolated from the entire splenocyte population demonstrated a similar suppression. Levels of thymic regulatory T-lymphocytes (T_{reg} cells; $CD4^+CD25^+Foxp3^+$) which regulate/suppress effector T-lymphocytes were increased in pups exposed prenatally to CS at 0, 1, and 8 d post-injection; splenic T_{reg} cell levels were also increased, but only on d 8. Prenatal CS exposure increased the amount of TGF-β released in both phorbol myristate acetate- and tumor cell-stimulated splenocyte cultures. The CS-induced increase in tumor susceptibility originally seen in prenatally-exposed offspring was ameliorated by depletion of $CD4^+CD25^+$ cells. Given that T_{reg} cells (and TGF-β) can suppress anti-tumor CTL activity, these findings suggest a possible mechanism by which fetal insult by CS could have resulted in reduced CTL activity in the offspring during tumor development. Taken together, these data suggest that children of smoking mothers may be less able to mount an appropriate immune response to tumors, thus increasing their risk for cancer development later in life.

POSTER #14

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THE TOXICITY OF INGESTED POLONIUM-210

Bobby R. Scott

Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108

The polonium-210 (Po-210) poisoning of Alexander Litvinenko in London in November 2006 stimulated interest around the world in the toxicity of Po-210. Mr. Litvinenko was a former detective and critic of the Russian government. Shortly after the London incident was reported in the news media, research was initiated at our Institute related to evaluating what constitutes a lethal intake of Po-210 via ingestion. At the time of the incident, it was suspected (and later confirmed) that intake was via ingestion. The Po-210 was apparently sprayed into the cup of tea that was ingested by Mr. Litvinenko in the Pine Bar of the Millennium Hotel. This presentation does not consider the specific radiological circumstances surrounding the tragic death of Mr. Litvinenko; rather, it provides results of an evaluation of what constitutes a lethal intake via ingestion. Key findings are as follows: (1) Ingestion of a few tenths of a milligram of Po-210 will likely be fatal to all exposed persons, (2) Lethal intakes are expected to involve fatal damage to the radiosensitive bone marrow which is likely to be compounded by damage caused by higher doses to other organs including the kidneys and liver, (3) Lethal intakes are expected to cause severe damage to the kidneys, spleen, stomach, small and large intestines, lymph nodes, skin, and testes (males) in addition to the fatal damage to bone marrow, and (4) The time distribution of deaths is expected to depend on the level of radioactivity ingested, with deaths occurring within about a month after very high levels of radioactivity intake (e.g., systemic burdens >1 MBq/kg-body-mass) and occurring over longer periods, possibly up to or exceeding a year for lower but lethal intakes (systemic burdens from 0.1 to 1.0 MBq/kg-body-mass). Below a systemic burden estimate of 0.02 MBq/kg-body-mass, deaths from deterministic effects are not expected to occur but the risk of cancer and for life shortening could be significant. For lethal intakes of Po-210, current remedial medical treatment strategies (e.g., chelation therapy) may not be successful, especially if there is a significant delay in applying the treatment. *The research was supported by Lovelace Respiratory Research Institute*.

POSTER #15

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MODULATION OF ENDOTHELIAL NITRIC OXIDE SYNTHASE FUNCTION BY ATMOSPHERIC POLLUTANTS

Jennifer Buntz, Selita Lucas, Matthew Campen. College of Pharmacy, University of New Mexico, Albuquerque, NM, 87131

Detrimental effects of vehicular emissions on the vascular system are increasingly recognized as important potential contributors to the overall cardiovascular disease risk. Our data show that diesel engine emissions (DE) can induce alterations in electrocardiographic indices that may represent inadequate coronary perfusion. Previously, we have shown that coronary arteries exhibited enhanced constriction to the peptide endothelin-1 (ET-1) after DE exposures. In this study, we have examined the effects of DE and two of the principal gaseous components thereof, nitric oxide (NO) and carbon monoxide (CO), on the level and function of a crucial vascular regulatory enzyme, endothelial nitric oxide synthase (eNOS). Healthy, male Sprague-Dawley rats were exposed whole body to DE (300 μg particulate matter [PM]/m^3), NO (10 ppm) or CO (30 and 100 ppm) for a single 4 or 5-hour period. Aortic eNOS protein was significantly elevated (~3-fold) following DE and NO exposures compared to that found in filtered air-exposed (FA) control rats. Further investigation revealed that while total NOS activity, measured by a citrulline formation assay, was elevated in the aortas of exposed rats, the activity to protein concentration ratio of NOS was reduced, suggesting dysfunction of this protein with a compensatory synthesis of new protein. Coronary artery constriction to ET-1 was enhanced following NO exposure in a manner similar to that seen in DE experiments. Carotid artery relaxation in response to acetylcholine was diminished in CO exposed rats. Thus, it appears that exogenous nitric oxide has the capacity to disrupt normal eNOS function, leading to compensatory molecular responses in endothelial cells. These studies 1) characterize a potentially crucial pathway underlying air pollution-induced endothelial dysfunction and 2) identify monoxide gases as potential environmental drivers of this effect.

POSTER #16

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APPENDIX B

Mountain West Society of Toxicology

Copies of Letters for Award

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12 August 2009

Request for Funding for Strategic Activities for MWSOT Regional Chapter

Submitted by Matthew D. Reed, MWSOT Vice-President, 2009

To Marcia Lawson, Liaison to Regional Chapters, and Whom It May Concern:

The Mountain West Regional Chapter strategic focus has been to engage, and expand member involvement in a forum where smaller groups can engage in scientific discussions of new approaches in toxicology. We feel this focus is aligned with SOT Strategic Plan priorities of: 1) building the future of toxicology and 2) expand and deepen member engagement. The MWSOT Regional Chapter has historically consisted primarily of members from academic institutions within the region. In addition, the geography of our region requires significant travel to our Annual Meeting. Therefore, we feel that it is imperative that we offer topics that are of interest to a broad constituency to ensure that we continue to engage and expand member involvement and provide insight into career opportunities that build on the future of toxicology in our trainees and students.

The significant travel time required for our Annual Meetings results in a longer meeting than some Regional Chapters, but this format allows for group discussions during scientific sessions as well as during "social" sessions. A goal for our chapter is to broaden the membership and provide trainees insight into industry (where most will likely reside after their training experience), in particular we would like to increase industry and other stake-holder involvement. While our region does not have large pharma or other large industrial centers with extensive toxicology infrastructure, there are several more modest-sized companies that we would like to reach out to and try to increase involvement in our Regional Chapter. Recently, our efforts in this regard have been to invite speakers from industry to provide scientific talks in the scientific sessions with our other invited speakers. Our current plans are to continue this practice; however, we would like to expand this effort by continuing a new sessions where we include speakers, both those invited by MWSOT and those sponsored by industry, that will speak to issues that are particularly important for industry, but that would also be instructive to our trainees and our highly academic audience.

This year's session is entitled, "***Industry and Career Perspectives.***"

The following speakers and plenary discussions include:

"The Importance of Discovery Work During the Drug Development Process"
Michael A. Dorato, Ph.D., D.A.B.T.
Vice President, Scientific and Technical Services
Covance Laboratories Inc.

"Contract Research Organizations in the 21st Century: The Integration of Business and Science"
Kevin J. Kerzee, PhD, DABT
Manager, Operations
Bioproducts for Science
Harlan Laboratories, Inc.
Research Models and Services
Indianapolis, IN

Sponsor
*"High Throughput Stem Cell Hemotoxicity Screening and Testing"**
Ivan N. Rich, PhD
Founder, Chairman & CEO
HemoGenix, Inc
1485 Garden of the Gods Road
Suite 152
Colorado Springs, CO 80907

"Application of Toxicogenomics and Pathway Analysis: Evaluation of Non-Alcoholic Fatty Liver Disease Models for Investigating Drug-Induced Liver Injury."
John W. Davis II, PhD
Director, Investigative Toxicology
PGRD
Pfizer, St. Louis

This lecture series continues to attract new industry involvement from within the region as well as related research disciplines that may not attend 'toxicology' meetings.

As our students and trainees are rarely exposed to industry careers, I would like to request funds to support this Strategic Activity effort. The funds will be utilized to continue this session by providing the resources to cover additional advertising, enhancing the scientific poster session, and providing an appropriate venue for 1-on-1 discussions of career opportunities in industry (banquet).

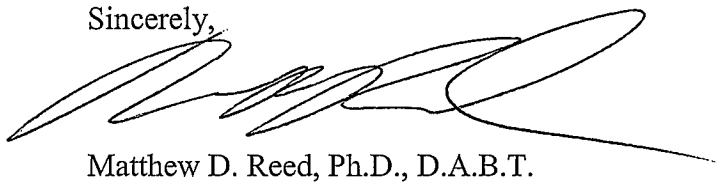
Assembly and disassembly costs of poster boards for scientific sessions are considerable at any meeting venue (the poster session and AV requirement are one of our largest annual meeting expenses, our anticipated costs for this activity are over $2000). We anticipate that increased member involvement will expand the poster session and so additional funds are needed. This funding will also help support a banquet after the poster session (supplemented by registration). This is another opportunity for stake-holders, trainees, investigators, and industry experts to engage in small groups. This banquet has been a fixture of our Annual Meetings but due to the financial situation of our Regional Chapter, we may not be able to offer this critical component of our meeting where scientific discussions naturally follow from the sessions earlier in the day.

These discussions promote scientific excellence in the toxicology research in our Region. These Strategic Activity funds would not be sufficient to cover the costs of both the poster session and the dinner but could substantially support these activities without being forced to substantially increase our registration costs, which we feel would have a

pronounced negative impact on member participation considering national funding levels at this time (Incidentally, we are already planning to raise our registration cost by ~%10).

Therefore, we request $2000 to continue development of our Strategic Activity to enhance the scientific session at our Regional Chapter meeting. Funds will be used to develop our Industry Education Workshop idea, that this year, will include speakers sponsored by Covance, invited by MWSOT (Pfizer and Harlan labs), and those attending the meeting (HemoGenix) as well as support the scientific poster session, and related social activities. Thank you for considering our request.

Sincerely,



Matthew D. Reed, Ph.D., D.A.B.T.

"Toxicology in the Development of Countermeasures for Radiation, Chemical, and Biological Threat Agents"

Keynote Presentation
"The Life Cycle of a Botulinum Toxin Molecule"
Lance L. Simpson, PhD
Professor Infectious Disease and Environmental Medicine
Thomas Jefferson Medical School, Philadelphia, PA

Plenary

"Ricin Toxicity and Pharmacokinetics Following Inhalation and Ingestion"
Janet M. Benson, PhD, DABT
Senior Scientist, Program Manager, Applied Toxicology
Lovelace Respiratory Research Institute
Albuquerque, NM

"Scientific Basis for Developing Approaches to Decorporating Internally Deposited Radionuclides"
Raymond A. Guilmette, PhD, FHPS, CRadP
Senior Scientist, Director, Center for Countermeasures Against Radiation
Lovelace Respiratory Research Institute
Albuquerque, NM

"*Acute and Chronic Effects of Sulfur Mustard"*
Gary R. Grotendorst, PhD
Senior Scientist, Respiratory Immunology and Asthma Program, Director CounterACT Research Center of Excellence
Lovelace Respiratory Research Institute
Albuquerque, NM

"Neuroimmune Effects of Sarin Inhalation"
Mojan L. Sopori, PhD
Senior Scientist, Respiratory Immunology and Asthma Program
Lovelace Respiratory Research Institute
Albuquerque, NM

Student Presentation

To Be Determined Based on Abstract Receipt

Topic II: Industry and Career Perspectives

***Diamond Sponsor Discussion**
"The Importance of Discovery Work During the Drug Development Process"
Michael A. Dorato, Ph.D., D.A.B.T.
Vice President, Scientific and Technical Services
Covance Laboratories Inc.

"Contract Research Organizations in the 21st Century: The Integration of Business and Science"
Kevin J. Kerzee, PhD, DABT

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1485 Garden of the Gods Road
Suite 152
Colorado Springs, CO 80907

(see below) "Applications of Toxicogenomics in Preclinical Safety Assessment"
John W. Davis II, PhD

Topic III: Systems Biology and Special Topics

"Application of Toxicogenomics and Pathway Analysis: Evaluation of Non-Alcoholic Fatty Liver Disease Models for Investigating Drug-Induced Liver Injury."
John W. Davis II, PhD
Director, Investigative Toxicology
PGRD
Pfizer, St. Louis

"Transcription Profiling of Nanometals Commonly Used in Consumer Products"
Philip Moos, PhD
Assistant Professor
Pharmacology and Toxicology, University of Utah

"Novel Mechanisms of Viral Pathogenesis Using a System-wide Approach"
Kevin Harrod, PhD
Director, Infectious Disease Program
Lovelace Respiratory Research Institute
Albuquerque, NM

"Correlation of the Physicochemical Characteristics of Engineered Nanomaterials to Cellular and Tissue-level Responses"
Rashi Iyer, PhD
Technical Staff Member
B-7, Biosecurity and Public Health
Los Alamos National Labs

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12 August 2009

Request for Funding for Student Travel to MWSOT Regional Chapter Meeting

Matthew D. Reed, MWSOT Vice-President (meeting organizer), 2009

To Marcia Lawson, Liaison to Regional Chapters, and Whom It May Concern:

The Mountain West Regional Chapter can be characterized as being predominantly academic in nature and geographically expansive. As such, it would be highly beneficial to our annual meeting to receive travel support from SOT Headquarters to enhance the number of students who can attend.

Typically, 25% of attendees come from each of New Mexico, Colorado, Utah, and Arizona, meaning that 50% of attendees will require an ~8 hour drive (for adjacent states) and 25% will require a ~14 hour drive (for diagonal states). We propose to utilize the funding for schools outside of the state containing the meeting locale. For 2009, we propose to provide funding to graduate or undergraduate students from Arizona, Colorado, and Colorado, for travel to the meeting in Albuquerque, NM. In addition, preference may be given to underrepresented schools (i.e. the "State" Universities in the region, as the majority of participants are from the University of Arizona, Colorado, New Mexico, and Utah) in the region in an attempt to increase participation at our Regional Meeting.

Our Regional Chapter meeting serves as an excellent primer for trainee presentations where there is an opportunity for feedback before the National SOT Meeting Abstract deadline. As stated above, our Chapter is highly academic and so participation in our meetings is required to maintain the vitality of our Chapter. Therefore, with current funding level restrictions, these travel funds can help maintain vitality of our meetings by allowing students to attend that may not otherwise be able to attend.

The process for determining the winners will include submission of the abstract, CV and a brief research summary for the MWSOT officers to judge, such that travel awards will represent an accolade that may enhance career opportunities. Clearly, a presentation, either oral or poster, will be necessary for consideration.

Therefore, we request $2000 for student travel to enhance our attendance and provide students with the opportunity to attend our regional chapter meeting. Funds will be provided to up to 8 students, who are otherwise unable to attend, in the order of $250 to defer the costs of travel and attendance; plus provide an opportunity to present their data in a talk or poster. Thank you for considering our request.

Sincerely,

Matthew D. Reed, Ph.D., D.A.B.T.

"Toxicology in the Development of Countermeasures for Radiation, Chemical, and Biological Threat Agents"

Keynote Presentation
"The Life Cycle of a Botulinum Toxin Molecule"
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Raymond A. Guilmette, PhD, FHPS, CRadP
Senior Scientist, Director, Center for Countermeasures Against Radiation
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Senior Scientist, Respiratory Immunology and Asthma Program
Lovelace Respiratory Research Institute
Albuquerque, NM

Student Presentation

To Be Determined Based on Abstract Receipt

Topic II: Industry and Career Perspectives

***Diamond Sponsor Discussion**
"The Importance of Discovery Work During the Drug Development Process"
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"Novel Mechanisms of Viral Pathogenesis Using a System-wide Approach"
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Rashi Iyer, PhD
Technical Staff Member
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12 August 2009

Request for Funding for Speaker Travel to MWSOT Regional Chapter Meeting

Submitted by Matthew D. Reed, MWSOT Vice-President, 2009 (meeting organizer)

To Marcia Lawson, Liaison to Regional Chapters, and Whom It May Concern:

The Mountain West Regional Chapter has consistently had high caliber speakers at our Annual Meetings to ensure that the science is exemplary and instructive for all members. We feel that this year is no different. The following speakers are traveling to our meeting and will provide direct impact to the plenary topic of the meeting as well as to educational and career opportunities for MWSOT scientific and trainee membership.

Plenary Lecture
"The Life Cycle of a Botulinum Toxin Molecule"
Lance L. Simpson, PhD
Professor Infectious Disease and Environmental Medicine
Thomas Jefferson Medical School, Philadelphia, PA

System's Biology
(Pharmaceutical Highlight)
"Application of Toxicogenomics and Pathway Analysis: Evaluation of Non-Alcoholic Fatty Liver Disease Models for Investigating Drug-Induced Liver Injury."
John W. Davis II, PhD
Director, Investigative Toxicology
PGRD
Pfizer, St. Louis

Interface of Business and Science- Contract Toxicology
"Contract Research Organizations in the 21st Century: The Integration of Business and Science"
Kevin J. Kerzee, PhD, DABT
Manager, Operations
Bioproducts for Science
Harlan Laboratories, Inc.
Research Models and Services
Indianapolis, IN

The scientific theme for the plenary session of our meeting is "Toxicology in the Development of Countermeasures Against Rad/Chem/Bio Threat Agents." **Dr. Phillip Simmons** will provide a holistic assessment of botulinum toxin in light of its impact as a toxicant and potential chem-bio warfare/ terror agent. Dr. Simmons compliments the selected scientific MWSOT speakers by providing an in depth look into the mechanistic

action of botulinum on mammalian and cell culture systems. His discussions and expertise directly enhance the primary meeting topic.

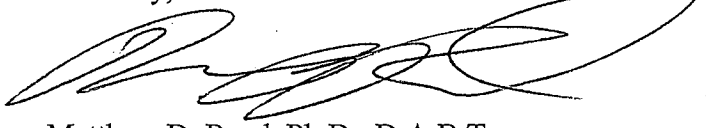
Dr. Davis combines discussions with Dr. Kevin Harrod of Lovelace and Dr. Philip Moos of the University of Utah by focusing on systems biology and biomarker development in the drug discovery process. Proteomic, genomic and metabolomic biomarker discovery is a focus of current rad-chem-bio funding efforts of the National Institutes of Allergy and Infectious Disease (NIAID), Department of Defense (DOD), and the Department of Homeland Security (DHS) as well as a standard for general concepts in toxicology research. The former are highly relevant funding sources that may not be readily known to the MWSOT membership. In addition, Dr. Davis highlights potential careers in the industry by providing what might be considered "academic-type" research paths in toxicology in an industry setting. Dr. Davis is an outstanding speaker and highly respective member of SOT. He is a co-founder and current President of the Drug Discovery Specialty Section of SOT.

Dr. Kevin A Kerzee Dr. Kerzee is a successful toxicologist in the contract research organization industry. Dr. Kerzee was trained under Dr. Kenneth Ramos while at Texas A&M University. Dr. Kerzee is currently the Manager, Operations Bioproducts for Science and has given a number of talks to students concerning the integration of science and business. Dr. Kerzee will compliment the student-career focused efforts of the meeting.

Considering the financial status of our Chapter, we have made an effort to identify outstanding speakers within our region to ensure that we control travel costs but focus on an important new research area. I have told speakers we will pay for travel, room and incidental costs associated with their trip to contribute to our meeting. We currently have $1000 committed from Lovelace for travel expenses. Our expectation based on current air fares is that the flights will cost approximately $600 per speaker, hotel accommodations per speaker are approximately $320, and between travel to the airports and food on the way, I expect another ~$200 in incidental costs. This adds up to ~$1120 per speaker, based on current costs for speaker travel that will truly help our Chapter put on a successful 27th annual meeting. We plan to offset the travel costs with ~$500 committed from VWR and Thermofisher.

Therefore, we request up to $2000 for speaker travel (due to fluctuating fuel costs) to enhance the scientific session at our Regional Chapter meeting. Funds will be used for travel and accommodations for these speakers. Thank you for considering our request.

Sincerely,



Matthew D. Reed, Ph.D., D.A.B.T.

"Toxicology in the Development of Countermeasures for Radiation, Chemical, and Biological Threat Agents"

Keynote Presentation
"The Life Cycle of a Botulinum Toxin Molecule"
Lance L. Simpson, PhD
Professor Infectious Disease and Environmental Medicine
Thomas Jefferson Medical School, Philadelphia, PA

Plenary

"Ricin Toxicity and Pharmacokinetics Following Inhalation and Ingestion"
Janet M. Benson, PhD, DABT
Senior Scientist, Program Manager, Applied Toxicology
Lovelace Respiratory Research Institute
Albuquerque, NM

"Scientific Basis for Developing Approaches to Decorporating Internally Deposited Radionuclides"
Raymond A. Guilmette, PhD, FHPS, CRadP
Senior Scientist, Director, Center for Countermeasures Against Radiation
Lovelace Respiratory Research Institute
Albuquerque, NM

"*Acute and Chronic Effects of Sulfur Mustard"*
Gary R. Grotendorst, PhD
Senior Scientist, Respiratory Immunology and Asthma Program, Director CounterACT Research Center of Excellence
Lovelace Respiratory Research Institute
Albuquerque, NM

"Neuroimmune Effects of Sarin Inhalation"
Mojan L. Sopori, PhD
Senior Scientist, Respiratory Immunology and Asthma Program
Lovelace Respiratory Research Institute
Albuquerque, NM

Student Presentation

To Be Determined Based on Abstract Receipt

Topic II: Industry and Career Perspectives

***Diamond Sponsor Discussion**
"The Importance of Discovery Work During the Drug Development Process"
Michael A. Dorato, Ph.D., D.A.B.T.
Vice President, Scientific and Technical Services
Covance Laboratories Inc.

"Contract Research Organizations in the 21st Century: The Integration of Business and Science"
Kevin J. Kerzee, PhD, DABT

Manager, Operations
Bioproducts for Science
Harlan Laboratories, Inc.
Research Models and Services
Indianapolis, IN

Sponsor
*"High Throughput Stem Cell Hemotoxicity Screening and Testing"**
Ivan N. Rich, PhD
Founder, Chairman & CEO
HemoGenix, Inc
1485 Garden of the Gods Road
Suite 152
Colorado Springs, CO 80907

(see below) "Applications of Toxicogenomics in Preclinical Safety Assessment"
John W. Davis II, PhD

Topic III: Systems Biology and Special Topics

"Application of Toxicogenomics and Pathway Analysis: Evaluation of Non-Alcoholic Fatty Liver Disease Models for Investigating Drug-Induced Liver Injury."
John W. Davis II, PhD
Director, Investigative Toxicology
PGRD
Pfizer, St. Louis

"Transcription Profiling of Nanometals Commonly Used in Consumer Products"
Philip Moos, PhD
Assistant Professor
Pharmacology and Toxicology, University of Utah

"Novel Mechanisms of Viral Pathogenesis Using a System-wide Approach"
Kevin Harrod, PhD
Director, Infectious Disease Program
Lovelace Respiratory Research Institute
Albuquerque, NM

"Correlation of the Physicochemical Characteristics of Engineered Nanomaterials to Cellular and Tissue-level Responses"
Rashi Iyer, PhD
Technical Staff Member
B-7, Biosecurity and Public Health
Los Alamos National Labs

APPENDIX C

Mountain West Society of Toxicology

Current SOT Ledger

WACHOVIA

Commercial Checking - Wholesale

01 2000003783953 072 130 0 38 52,736

00019568 01 AV 0.335 01 5DGS 78

MOUNTAIN WEST CHAPTER
SOCIETY TOXICOLOGY CB
1821 MICHAEL FARADAY DR.,STE 300
RESTON VA 20190

Commercial Checking - Wholesale

7/01/2010 thru 7/30/2010

Account number: 2000003783953
Account owner(s): MOUNTAIN WEST CHAPTER
SOCIETY TOXICOLOGY

Account Summary

Opening balance 7/01	$18,145.60
Deposits and other credits	2,420.00 +
Closing balance 7/30	**$20,565.60**

Deposits and Other Credits

Date	*Amount*	*Description*
7/06	2,000.00	DEPOSIT
7/30	170.00	DEPOSIT
7/30	250.00	DEPOSIT
Total	**$2,420.00**	

Daily Balance Summary

Dates	*Amount*	*Dates*	*Amount*	*Dates*	*Amount*
7/06	20,145.60	7/30	20,565.60		