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Michigan Regional Chapter of the Society of Toxicology

NEWSLETTER

Volume 22

Number 1

January, 2004

Editor: Lawrence H. Lash

Associate Editor: Randall J. Ruch

MESSAGE FROM THE PRESIDENT

(submitted by Robert Meeks)

Greetings to all. I hope every one of you had a great holiday season and I wish you a very peaceful 2004. I want to thank all of you that attended our Fall meeting in Lansing. It was a great program at a great facility. I personally thought it was well attended and that the presentations were educational and stimulating. All of the posters were of high quality. It certainly made the judging a tough task evidenced by the fact that there was a tie for first place among the graduate student posters. My thanks to Steve Frantz for bringing this together. Steve also has promised a great spring meeting, which is planned at a great venue. Stay tuned for the meeting announcement and the agenda for that program. My only hope is that the snow is gone and the weather is warm by then. Finally, I would like to remind all of you that if you haven't already done so, please take a minute and register for the national meeting in Baltimore, which is being held March 21-25. I look forward to seeing all of you there.

Spring Meeting Preview

(contributed by Steve Frantz)

MPI Research will be sponsoring the Spring meeting of the Michigan Chapter of SOT. The topic is still being developed. The venue will be the Michigan State University Brook Lodge facility (recently donated to MSU by Pharmacia/Upjohn). It should be an interesting venue. Look for more details soon!

Student/Post-doc News

(contributed by Jim Luyendyk)

MISOT Members,

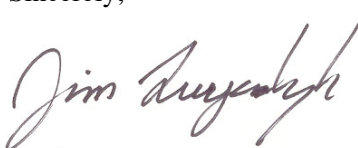
This will be my last formal contribution to the MISOT Newsletter. My term as MISOT Representative to SOT's Student Advisory Committee (SAC) will be ending in May of this year. I have greatly enjoyed the last two years, and I would like to thank the MISOT membership for granting me this opportunity. In the past two years we have seen continued growth of MISOT's Student Membership and poster sessions at our Chapter's meetings. One of several new highlights for our Student Membership is the new Post-doctoral poster award presented at the Fall meeting. The winner of this award receives \$200 and is invited to give a 20-minute presentation at the Spring meeting. The winner of the first annual Post-doctoral award in 2003 was XinWen Yu from Pfizer.

The selection process for MISOT Student Advisory Committee Representative for 2004 has already started. This process for MISOT has not been formalized and will be based on an appointment by MISOT Council. The newly appointed MISOT Representative will work with MISOT Council to integrate the SAC's recently revised Suggested Guidelines for Representative Selection into MISOT's selection process in 2004. Our hope is to have an election-based system in place for Spring 2005.

With the assistance of our Council, MISOT remains focused on recruitment and retention of its Student Membership. I fully expect that this enthusiasm will continue during the transition of SAC Representatives within the chapter.

Advisors, make sure to remind your students to **join MISOT!** For more information, visit: <http://www.toxicology.org/memberservices/regionalchapter/michigan/misot.html>

Sincerely,



Jim Luyendyk

CHAPTER MEMBER PROFILE



Rudy J. Richardson, ScD, DABT, is the Dow Professor of Toxicology in the Department of Environmental Health Sciences, School of Public Health, and Associate Professor of Neurotoxicology in the Neurology Department, School of Medicine, at the University of Michigan. Dr. Richardson has been a member of the University of Michigan faculty since 1975 and has had an illustrious career there.

Dr. Richardson graduated *magna cum laude* with a Bachelor of Science degree in Chemistry from Wichita State University in 1967. He then completed the Master of Science and Doctor in Science degrees in Physiology/Toxicology in 1973 and 1974, respectively, at Harvard University. His postdoctoral training was as a Research Scientist in Neurochemistry/Neurotoxicology at the Medical Research Council (MRC) Toxicology Unit in Carshalton, Surrey, UK from 1974-75.

Chapter Member Profile (continued)

Immediately following his postdoctoral experience, he joined the faculty of the University of Michigan as an Assistant Professor of Toxicology. He has subsequently been very successful as a scientist, teacher, and administrator, achieving full Professorship in 1984, and being named to the Dow Professor of Toxicology endowed chair in 1998. He is also currently Director of the NIEHS-funded Environmental Toxicology Training Program in the School of Public Health and has been a Diplomate of the American Board of Toxicology since 1984.

Dr. Richardson has had an outstanding research career and has become a leader in the neurotoxicology field. His research interests fall under the general category of mechanistic pharmacology and toxicology with applications to drug discovery. His work focuses on discovering and characterizing relevant molecular targets and networks for defined biological responses to understand pathogenesis and invent preventive and therapeutic strategies for neurological and other disorders. He is also developing biomarkers of xenobiotic exposure and neural disease and investigating interactions between xenobiotics and macromolecular targets using kinetics, computational modeling, proteomics, and mass spectrometry. He is applying these approaches to counterterrorism by developing biomarkers and biosensors for novel chemical agents. Additionally, Dr. Richardson has been very active and successful in forging local, national, and international research collaborations among scientists across a range of physical and biological disciplines especially between US and Russian scientists. Support for these efforts has been copious and garnered from the EPA, NIH, US Army, Dow Chemical Company, CIPHERGEN Biosystems, and other public and private institutions and agencies. Dr. Richardson has published extensively in neuroscience and toxicology journals. A recent publication [Doorn, J.A., Schall, M., Gage, D.A., Talley, T.T., Thompson, C.M., and Richardson, R.J. (2001) Identification of butyrylcholinesterase adducts after inhibition with isomalathion using mass spectrometry: Difference in mechanism between (1R)- and (1S)-stereoisomers. *Toxicol. Appl. Pharmacol.*

176, 73-80] won the 2003 Society of Toxicology Board of Publications Award for Best Paper in *Toxicology and Applied Pharmacology*.

Dr. Richardson's scientific expertise and reputation is further exemplified by his prolific extramural scientific service. He has served as reviewer, consultant, expert witness, invited speaker, and committee member for national and international agencies and institutions that include the National Academy of Sciences, NIH, NIOSH, NSF, USEPA, ILSI, MRC, and WHO. Most recently, he has been a Foreign Collaborator with the International Science and Technology Center and the US Civilian Research and Development Foundation in their efforts to develop scientific collaborations between the United States and Russia. He also was an Invited Scientist to a joint US CDRF-Russia workshop on research to minimize the effects of terrorist acts on civilian populations.

Dr. Richardson is a member of many scientific and professional organizations that include the American Chemical Society, American College of Toxicology, the American Society for Neurochemistry, the Society of Neuroscience, and the Society of Toxicology. In the SOT, Dr. Richardson has served the Neurotoxicology section as President, Vice-President, Chairman of the Program Committee, and Councilor. He is also a member of the Michigan Chapter of the SOT and has served as Vice-President, Councilor, and member of the Nominating Committee. He has been named to the editorial boards of *Journal of Toxicology and Environmental Health*, *Neurotoxicology*, *Toxicology and Applied Pharmacology*, and *Toxicology and Industrial Health*.

Dr. Richardson has an equally impressive record in graduate education. He has focused his teaching activities primarily in the Toxicology Program in the School of Public Health where he has been a lecturer or the Director for numerous courses. He has also been a guest lecturer at Wayne State University, Michigan State University, the University of Padua, the University of Montana, the University of Connecticut, the University of California at San Diego, the University of Minnesota, and the Mayo Clinic Medical School. He has been the mentor or major advisor for three undergraduate students, 28 MS/MPH students, 21 PhD students,

Chapter Member Profile

(continued)

seven postdoctoral fellows, and nine senior research staff. As noted above, he is also currently the Director of the NIEHS-funded Environmental Toxicology Research Training Program that the School of Public Health has held for over 20 years.

Dr. Richardson is married (Kathleen) and has three children (Anne, Olivia and Gavin). In what little spare time he can sequester, he plays classical guitar and enjoys old movies (the 1940s is his favorite era) and Star Trek episodes (New Generation) with his family. He is also an avid reader and has recently enjoyed *Uncle Tungsten*, *The Passion of Artemesia*, *Pablo Neruda: Selected Poems*, and *Prime Obsession* (about the Riemann hypothesis). He adds that when he wants to see something truly clever, he catches an episode of *Sponge Bob*.

Winning Abstracts from Fall, 2003 Meeting:

**Darrell Boverhof and James Luyendyk
(TIE): Student award Winner**

Ethynyl estradiol elicited temporal and dose-dependent hepatic gene expression patterns in immature, ovariectomized mice

D.R. Boverhof^{1,2}, K.C. Fertuck^{1,2}, L.D. Burgoon^{2,3}, J.E. Eckel⁴, C. Gennings⁴ and T.R. Zacharewski^{1,2,3}.

¹Dept of Biochemistry & Molecular Biology, ²Institute for Environmental Toxicology, and ³Dept of Pharmacology & Toxicology, National Food Safety & Toxicology Center Michigan State University; ⁴Dept of Biostatistics, Virginia Commonwealth University.

Temporal- and dose-dependent changes in hepatic gene expression were examined in immature ovariectomized C57BL/6 mice gavaged with ethynyl estradiol (EE). For temporal analysis, mice were gavaged every 24 hrs for 3 days with 100 $\mu\text{g}/\text{kg}$ EE or vehicle and liver samples were collected after 2, 4, 8, 12, 24 and 72 hr. Gene expression was monitored using custom cDNA microarrays containing 3068 cDNA clones of which 393 exhibited a significant change at one or more time points as determined using a model-based t-statistic

filtering approach. Functional gene annotation extracted from public databases provided an association between temporal gene expression changes and physiological processes such as growth and proliferation, cytoskeletal and extracellular matrix responses, microtubule based processes, oxidative metabolism and stress, and lipid metabolism and transport. In the 24-hr dose-response study, hepatic samples were collected from mice treated with 0, 0.1, 1, 10, 100 or 250 $\mu\text{g}/\text{kg}$ EE. Thirty-nine of the 79 genes identified as differentially regulated at 24 hr in the time course study exhibited a dose response relationship with ED_{50} values ranging from 1.5 to 2100 $\mu\text{g}/\text{kg}$ with an average of 47 ± 3.5 $\mu\text{g}/\text{kg}$. Comparative analysis indicated that many of the identified temporal and dose-dependent hepatic responses are similar to estrogen-induced uterine responses reported in the literature and in a companion study using the same animals. Results from these studies confirm that the liver is a highly estrogen responsive tissue that exhibits a number of common responses shared with the uterus as well as distinct estrogen mediated profiles. These data will further aid in the elucidation of the mechanisms of action of estrogens in the liver as well as in other classical and non-classical estrogen responsive tissues. Supported by NIH Grant ES011271.

Altered gene expression as a contributing factor to liver injury in rats cotreated with ranitidine and lipopolysaccharide.

James P. Luyendyk¹, William B. Mattes², Jane F. Maddox¹, Gregory N. Cosma², Patricia E. Ganey¹, and Robert A. Roth¹

¹Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI, USA

²Investigative Toxicology, Pharmacia Corp., Kalamazoo, MI, USA

Studies in rats have suggested a role for underlying inflammation in idiosyncratic liver injury from the histamine 2-receptor antagonist ranitidine (RAN). Coadministration of nonhepatotoxic doses of RAN and the inflammagen, bacterial lipopolysaccharide (LPS), to rats results in hepatocellular injury. We tested the hypothesis that hepatic gene expression changes could distinguish Vehicle-, LPS-, RAN-, and LPS/RAN-treated rats before the onset of significant liver injury in LPS/RAN-treated rats (i.e., 3 h post-treatment). Rats were treated with LPS (44×10^6 EU/kg, iv) or its vehicle, then two hours later with RAN (30 mg/kg, iv) or its vehicle. They were killed 3 h after RAN treatment, and liver samples were taken for

evaluation of liver injury and RNA isolation. Hepatic parenchymal cell injury as estimated by increases in serum alanine aminotransferase (ALT) activity was not significant by 3 h. Hierarchical clustering of gene expression data from Affymetrix U34A rat genome arrays grouped animals according to respective treatments. Relative to vehicle-treated controls, treatment with RAN and/or LPS altered hepatic expression of numerous genes, including ones encoding for products involved in inflammation, hypoxia, and cell death. Some of them were enhanced synergistically by LPS/RAN cotreatment. Within this latter group, real-time PCR confirmed robust changes in expression of B-cell translocation gene 2, early growth response-1, and plasminogen activator inhibitor-1 (PAI-1) in cotreated rats. Consistent with the antifibrinolytic activity of PAI-1, significant fibrin deposition occurred only in livers of LPS/RAN-treated rats. This result suggests that expression of PAI-1 promotes fibrin deposition in liver sinusoids of LPS/RAN-treated rats and is consistent with the development of localized ischemia and consequent tissue hypoxia.

Shaila Kulkarni (Pfizer): Research Staff award

Quantitative mRNA invader analysis as a fast method to screen for induction potential of drugs using primary cultures of human and rat hepatocytes

Vsevolod Kostrubsky, Shaila Kulkarni, Janean Hanson and Steven Duddy,
Dept. of Safety Sciences, Pfizer, Ann Arbor MI 48105.

Using primary cultures of human and rat hepatocytes we investigated whether Invader mRNA (Third Wave Technology, Inc) analysis can be used as a fast method to study induction potential of drugs and whether changes in mRNA expression would associate with changes in appropriate enzyme activity and protein expression. Cultured hepatocytes were treated with beta-naphthoflavone, dexamethasone (Dex), rifampicin, phenobarbital (PB) and chenodeoxycholic (CDCA) acid for 48 h, and mRNA expression of CYP1A2, CYP3A4, CYP3A, CYP2B1/2, and biliary transporters, BSEP and MRP2, were analyzed. Corresponding enzymatic activities and protein expression were also measured. Different quantities of total RNA isolated from induced and control cells, as well as

positive control mRNA, produced linear responses as detected by Invader. The specificity of detection was validated via exposing cells to positive or negative control inducers as well as in cells transfected with genes of interest. Increases of 8-, 12-, 6-, 30-, 30- and 3-fold in CYP3A4, rat CYP3A (Dex), rat CYP3A (PB), CYP2B1/2, CYP1A2 and human BSEP mRNA, respectively were detected. Increases in mRNAs correlated with increases in enzymatic activities and protein expression, though the increases in enzyme activities were generally smaller magnitude relative to corresponding mRNAs suggesting that the sensitivity of mRNA detection is greater than changes in activities. These data suggest that the mRNA Invader assay provides fast (3 h, 96-well plate), quantitative and sensitive method for evaluation of different mRNA expression profiles.

XinWen Yu: Post-Doctoral award

NMR-based metabonomics as a tool in investigating CI-1034-evoked acute coronary artery injury in dogs

XinWen Yu¹, Michael D. Reily², J. Eric McDuffie¹, Donald Robertson¹ and Mudher Albassam¹. ¹Worldwide Safety Sciences, ²Discovery Technologies, Pfizer Global Research and Development, Ann Arbor, MI.

The objective of this study was to investigate the use of nuclear magnetic resonance (NMR) in acute coronary vascular injury evoked by CI-1034, a selective endothelin A receptor antagonist. CI-1034 was administered to male beagle dogs intravenously (iv) for 4 days. Treated groups consisting of 4 animals received CI-1034 at 120 mg/kg (iv) in bolus. Control animals (n=2) received the vehicle only. Animals were sacrificed on day 5. Macroscopically, hemorrhage was observed in the right coronary groove and right atrium of the CI-1034-treated animals. Histologically, coronary changes were noted in the CI-1034-treated dogs only and characterized by medial hemorrhage and necrosis, and mixed inflammatory-cell infiltrates in the adventitia and media. Increased levels of plasma fibrinogen, serum amyloid A (SAA) and IL-6 were detected using ELISA in CI-1034-treated dogs. Metabonomic analysis was conducted on urine and serum samples. Principal component pattern separation between control samples and samples from dogs treated with CI-

1034 were evident. In addition, the level of individual endogenous metabolites changed in a dose-dependent way and could be measured directly from the NMR spectra. This study showed for the first time that NMR may serve as a tool to investigate compound-evoked acute coronary injury using serum and urine samples from dogs.

Michigan Regional Chapter of the Society of Toxicology Annual Report 2003

I. Introduction

Active membership of 116 persons for 2003; including 85 full members and 31 student members.

	2002-2003	2003-2004
President:	Michael Graziano	Robert Meeks
President-Elect:	Robert Meeks	Stephen Frantz
Secretary/Treasurer:	John J. LaPres	John J. LaPres
Councilors:	Kathleen P. Plotzke Marc Bailie Don Robertson James G. Wagner	Michael Graziano Julie C. McGonigal Paul A. Jean James G. Wagner
Student Representative:	James Luyendyk	James Luyendyk
Newsletter:	Lawrence Lash (editor) Randall Ruch (co-editor)	

II. Activities

The 2002 Fall meeting was held on Friday, November 1, 2002 at the Kellogg Center on the campus of Michigan State University. The meeting was a joint meeting with the Midwest Teratology Association (MTA) and focused on Endocrine Disruptors. Featured speakers included Dr. Goerge Daston from P&G, who presented an overview of endocrine disruptors, their potential problems and new ways of addressing this environmental concern. Dr. Timothy Zacharewski (Michigan State

University) gave an overview of how to use the emerging field of toxicogenomics to address endocrine disruptors and some recent research his laboratory has performed in this field. Dr. Markus Hecker (Michigan State University) addressed the question of the environmental impact of these compounds and their effects on fish populations in the wild. Dr. Mel Anderson from CIIT closed the meeting by discussing the role of systems biology in endocrine disruptor research and offered some recent work from his laboratory. Dr. Dan Sheehan from NCTR was also scheduled to talk about the inadequacy of threshold models in toxicology, but was unable to attend the meeting due to illness. There were 139 registrants for the meeting: 134 of these attended the meeting, including 70 members, 32 students and 32 non-members.

The poster competition at the Fall meeting was also well attended with 16 abstracts submitted for judging. This enthusiasm was spurred in part by Jim Luyendyk's (student liaison) tireless effort and the \$1,000 prize in two categories. Janeen Hanson (Pfizer) won the Technical support category for her poster entitled: "Effect of Cholestatic Compounds on Canalicular Efflux and Cellular Uptake of Bile Acids in Cultured Human Hepatocytes." The student category was won by Belinda Hawkins for her poster entitled: "Cyproheptadine-Induced Inhibition of Preproinsulin mRNA Translation in Rinm5f Cells."

The 2003 Spring meeting was held on May 16, 2003 at the Dana Center on the campus of the Medical College of Ohio. The topic of this symposium was "Issues in Cardiovascular Toxicology." Speakers included Dr. Carrie Branch from Pharmacia, who spoke on *in vivo* approaches to assessing cardiovascular toxicity, Dr. Zi-Jian Xie from the Medical College of Ohio, who addressed the involvement of reactive oxygen species in ouabain-induced hypertrophic growth in cultured cardiac myocytes, Dr. Ken Wallace from the University of Minnesota-Duluth, who discussed Doxorubicin-induced mitochondrial cardiomyopathy, Dr. Brandi Soldo from Pfizer, who discussed Non-Cardiac Drug Interactions with Cardiac Ion Channels, and finally, Dr. Gene Herman from the FDA discussed the use of Troponin as a biomarker of myocardial injury. There were 32 meeting

participants including 13 members, 2 students and 17 non-members.

The Chapter again elected to support the Michigan Society for Medical Research (MISMR) by continuing our supporting institution membership.

III. Financial Status

INCOME STATEMENT (For the year ended July 31, 2003)

Income:

Deposits: \$9,989.68
These include dues, meeting registrations and MiSMR joint meeting funds

Expenses:

Meeting Expenses	
Fall	\$9,488.54
Spring	\$4,167.95
Newsletter	\$ 384.20
Travel award to SAC student	\$ 250.00
Supporting Institution (MISMR)	\$ 350.00
Officer's Meeting	<u>\$ 81.84</u>
Total Expenses	\$14,722.53
Net Income:	-\$4,732.85
Fund Balance, July 31, 2002	\$15,541.01
Fund Balance, July 31, 2003	\$10,808.16

IV. Future Plans

MISOT plans to continue to organize two scientific meetings each year; however, there is increasing awareness that it is difficult for scientists, particularly academicians, to attend numerous extracurricular meetings. Consequently, MISOT may continue to organize jointly with other regional professional societies with mutual interests. A primary goal in the planning of these meetings will be to increase student involvement.

The immensely positive feedback for our efforts to include technical support staff in our annual meetings has led us to continue these efforts. The primary goal is to increase membership in the chapter and obtain a different perspective on

toxicology related issues. In addition, the chapter has begun a recruiting drive to the less-represented Michigan universities and colleges in an attempt to increase their participation.

MISOT also plans to continue to develop our newsletter and circulate it three times a year. The MISOT also plans on using the National website and its links to regional chapters to increase involvement in the chapter and efficiency in communication with its members.

MEMBERSHIP NEWS

News items about activities involving our members are invited for this section.

Submissions for this section are encouraged!

MEMBER ABSTRACT OF RECENTLY PUBLISHED PAPER

Submissions for this section are encouraged!

APRIL ISSUE PREVIEW

The April, 2004 Issue of the Newsletter will feature details on the Spring meeting and other items of interest to our members.

Please submit any member news or ideas for the newsletter to your local contact person or directly to the editors. Material for the April newsletter should be submitted no later than March 29, 2004.

BENEFITS OF MEMBERSHIP

Don't forget that your membership to the Michigan Regional Chapter of the SOT includes:

- Discounted registration fees for chapter meetings
- Newsletter with chapter and regional news
- Free listing in the newsletter of training and employment opportunities
- Free listing in the newsletter of positions desired

POSITIONS AVAILABLE

Postdoctoral fellowships, research assistantships, government positions, and industrial positions can be advertised in this space. Submissions to the editor should include a brief description of the position and contact information. This service is free to members!

POSITION DESIRED

Individuals seeking positions in the region can advertise in this section. Submissions to the editor should include a brief description of research interests, experience, education, type of position desired, and geographical location desired. This service is free to members!

RESEARCH ASSOCIATE POSITION INFLAMMATION AND DRUG TOXICITY

A **RESEARCH ASSOCIATE POSITION** is available for the study of inflammation as a determinant of sensitivity to chemical toxicity. The research project deals with a novel hypothesis regarding the potential role of inflammation in adverse drug reactions, especially drug idiosyncrasy. Modern laboratories in the new National Food Safety and Toxicology Center at Michigan State University provide an excellent, interactive learning environment that includes access to state-of-the-science technologies and to expertise of productive faculty in a wide variety of disciplines. The project focuses on cellular mechanisms of interaction between drugs and inflammatory cells employing cell culture techniques and biochemical and molecular approaches. Applicants should have a **PhD. degree** or equivalent, training in cell/molecular biology and interest in at least one of the following areas: hepatic toxicology, drug-induced tissue injury, mediators of inflammation. Preference will be given to those eligible for support from an NIH training grant. Applications should include a resume that details the applicant's training, experience and interests and that includes names, addresses and phone numbers of three references. Please direct inquires to Dr. Patricia Ganey or Dr. Robert Roth, National Food Safety and Toxicology Center, Michigan State University, E. Lansing, MI 48824; e-mail: ganey@msu.edu or rothr@msu.edu.

This newsletter is published three times a year (January, April, and September) by the Michigan Regional Chapter of the Society of Toxicology. Send material for newsletter one month in advance by phone, fax, or e-mail to either:
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