BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Monica Valentovic, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): Valentovic

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Michigan Technological University	B.S.	05/1978	Chemistry
University of Toledo	M.S.	06/1980	Pharmacology
University of Kentucky	Ph.D.	12/1983	Pharmacology

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

Obesity is a serious health condition within the United States that contributes to increasing the risk of other disease. The current statistics have reported that 33% of Americans are obese. In West Virginia the incidence of obesity is over 35%. Postmenopausal women who are obese have a higher risk of developing breast cancer. It is anticipated that almost 232,000 women will be diagnosed with breast cancer in 2015 and many of these individuals will be obese. The mechanism for the increased risk of cancer in obesity is not known and probably is mediated through a complex interaction of various factors. New treatment modalities are needed to address reducing the development of breast cancer.

My educational background has provided an emphasis on pharmacology, pharmacokinetics, drug metabolism and toxicology. I have published over 91 research papers, over 150 abstracts and 4 book chapters on drug pharmacokinetics, toxicity and metabolism of xenobiotics. My graduate education provided a strong background in the area of drug metabolism as well as toxicology. My graduate education included experience with measurement of drug metabolism and pharmacokinetics in cell culture, human samples as well as rodent models. I have considerable experience with HPLC analysis of drugs, biomarkers of oxidative stress, endogenous substances (prostaglandins, ADP and ATP) as well as cellular markers of toxicity. We have considerable experience examining alterations in proteins due to toxicity. My laboratory has 2 Alliance Waters HPLC systems that are dedicated to analysis of pharmaceutical agents, endogenous substances and toxins. Our laboratory is active in examination of the mechanisms of toxicity of drugs and environmental agents in vivo as well as in vitro. I have 91 research publications in the area of pharmacology and toxicology and which provides a strong expertise to direct the studies examining leucine and other amino acids in cell culture media and cell samples. The selected papers in this section depict past experience with antibiotics, HPLC analysis as well as respiratory effects of pulmonary toxins such as ozone and cigarette smoke. The papers below also demonstrate our past experience at examining post-translational modifications of proteins due to increased oxidative stress using HPLC system. I want to mention that I have been on numerous NIH study sections and have Chaired more than 6 NIH study sections which reflects my competency as perceived by my professional

colleagues. I also was the 2013 recipient of the **Marshall University Distinguished Artist and Scholars Award in Science and Technology** award which is given to a faculty member as an achievement of research activity.

1. **M. Valentovic,** W. Lubawy. Active and passive cigarette smoking influences aortic PGI2 and platelet TXA2 synthesis in female rats. Res. Commun. Subst. Abuse 5(3): 233-239, 1984.

2. **M.A. Valentovic**, J.G. Ball and D.K. Anestis. Contribution of acetone and osmotic- diuresis to attenuation of cephaloridine nephrotoxicity by streptozotocin-induced diabetes. Toxicology 71:245-255, 1992.

3. J.L. Szarek and **M.A. Valentovic**. Release of prostaglandin in E2 and Leukotriene C4/D4 from airway segments isolated from rats after exposure to ozone for 20 months. Toxicology 100:111-119, 1995.

4. J.M. Brown, JG Ball, A Hogsett, T. Williams and **M.A. Valentovic**. Temporal study of acetaminophen (APAP) and S-adenosyl-L-methionine (SAMe) effects on subcellular hepatic SAMe levels and methionine adenosyltransferase (MAT) expression and activity. Toxicol Appl Pharmacol. 2010 Aug 15;247(1):1-9.

B. Positions and Honors

Employment

1983-1984 Postdoctoral fellow, University of Kentucky, College of Pharmacy
1984-1989 Assistant Professor, Dept of Pharmacology, Marshall Univ. School of Medicine
1989-1994 Associate Professor, Dept. of Pharmacology, Marshall Univ. School of Medicine
1994-Present Professor, Dept. of Pharmacology, Marshall Univ. School of Medicine

Professional Memberships, Honors and Experiences

Society of Toxicology
American Society of Pharmacology and Experiment Therapeutics
American Society of Nephrology
1997-present Editorial Board, J Toxicology and Environmental Health
2002-current Presidential Council of Alumni, Michigan Technological University
2013-present ASPET, Division of Toxicology Communication Liaison
2000-2001 Society of Toxicology, In Vitro Specialty Section, Vice President Elect
2001-2002 Society of Toxicology, In Vitro Specialty Section, Vice President
2002-2003 Society of Toxicology, In Vitro Specialty Section, President
1999-2004 NIH Ad Hoc Reviewer, NCI, DIG, SBIR, Drug Development and Drug Discovery
2004-2006 Society of Toxicology, Mechanisms Specialty Section, Secretary/Treasurer
2005 NIH Reviewer NIDDK ZDK1 GRB-N (01) RFA DK-05-001 July 2005
2005-2007 NIH Ad Hoc Reviewer ZRG1 DIG-A (10)
2006-2007 NIH **Chair** Study Section ZRG1 DIG-A July 2006; March 2007, Nov 2007
2007 NIH Reviewer NIDDK RFA DK-06-004 April 2007
2009 NIH Reviewer NIDDK ZRG1 DKUS-E (10) B March 24-25, 2009, March 18-19
2010 NIH Reviewer NCI N01-CM-07014-39 Preclinical Pharmacokinetics
2011 NIH Reviewer NIDDK ZRG1 DKUS-E (10)B March 13-14 (**Co-Chair**) , July 19-20 (**Chair**)
2012 NIH Reviewer NIDDK ZDK1 GRB-N (M6) March 30, 2012
2013 NIH Reviewer NIDDK ZDK1 GRB-N (M2) March 13-15, 2013
2013 Marshall University Distinguished Artist and Scholars Award in Science and Technology
2014 NIH NIDDK1 GRB-B (M1) April 25, 2014
2014 NIH NIDDK HPPP June 16-17, 2014
2014 NIH NIDDK HPPP November 4, 2014
2014 NIH NIDDK ZDK1 GRB-2 (J3) December 1, 2014
2015 NIH NIDDK 2015/08 ZDK1 GRB-B (M2) April 24, 2015
2015 NIH NIDDK ZDK1 GRB-7 (J2) November 19, 2015

C. Contribution to Science

Briefly describe up to five of your most significant contributions to science. For each contribution, indicate the historical background that frames the scientific problem; the central finding(s); the influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology; and your specific role in the described work. For each of these contributions, reference up to four peer-reviewed publications or other non-publication research products (can include audio or video products; patents; data and research materials; databases; educational aids or curricula; instruments or equipment; models; protocols; and software or netware) that are relevant to the described contribution. The description of each contribution should be no longer than one half page including figures and citations. Also provide a URL to a full list of your published work as found in a publicly available digital database such as SciENcv or My Bibliography, which are maintained by the US National Library of Medicine.

1. **We have examined cisplatin induced renal toxicity in diabetes**. We have focused on drug induced alterations mediated by cancer chemotherapy drugs. We showed that attenuation of cisplatin nephrotoxicity occurs in an experimental diabetic rat model. The first author was my graduate student who has gone on to a very successful international industrial career. We published several studies which documented that attenuation could not be attributed to marked diuresis and was mediated by cellular mechanisms**.** Although increased urine output due to the diabetic condition may be a mechanism, our studies showed that glucose induced diuresis can not account for the reduced toxicity. Our studies were a collaborative effort with Dr. Bob Yokel at the University of Kentucky who assisted in measuring renal and urinary Platinum levels. Most studies prior to our publication examined longer windows or renal accumulation at 24 or 48 h and we examined much earlier levels.
    a. L.A. Scott, E. Madan and M.A. Valentovic. Attenuation of cisplatin nephrotoxicity by streptozotocin (STZ) induced diabetes. Fundamental Appl. Toxicol. 12(3): 530-539, 1989.
    b. L.A. Scott, E. Madan and **M.A. Valentovic**. Effect of streptozotocin (STZ) diabetes, dextrose diuresis and acetone on cisplatin nephrotoxicity in Fischer 344 rats. Toxicology 60:109-125, 1990.

2. **Examination of oxidative stress by drugs and environmental chemicals:** I selected the papers in this section to highlight the antioxidant protection by RES for cisplatin nephrotoxicity. These studies show that RES preserves antioxidant enzyme activity despite exposure of renal slices to cisplatin. The co-authors on this paper include 3 undergraduates who went on to medical school as well as 2 graduate students who have graduated and are working as a hospitalist and as a toxicologist industry. The second paper focused on the oxidative stress mediated by 4-aminophenol and how addition of pyruvate to renal cortical slices reduced nephrocytotoxicity. 4-Aminophenol is a metabolite of acetaminophen and it is a byproduct of many hair dye prodcuts on the market. In excess aminophenol can induce renal toxicity. This study was part of my graduate student's dissertation. Dr. Harmon was a M.D./Ph.D. graduate and currently is a gastroenterologist in Colorado.
    a. M.A. Valentovic, J.G. Ball, J.M. Brown, M.V. Terneus, E. McQuade, S. Van Meter, H.M. Hedrick, A.A. Roy, T. Williams. Resveratrol Attenuates Cisplatin Renal Cortical Cytotoxicity by Modifying Oxidative Stress. Toxicology In Vitro 28:248-257, 2014.
    b. R.C. Harmon, K.K. Kiningham and **M.A. Valentovic.** Pyruvate reduces 4- aminophenol in vitro toxicity. Toxicol. Appl. Pharmacol., 213(2):179-86.2006.

3. **Examination of post translation modifications of proteins due to oxidative stress.** Our research demonstrated post-translational modifications by 4-Hydroxynonenal (4HNE) following acetaminophen overdose in mice. This paper examined oxidative stress in the liver of mice treated with acetaminophen. We have several publications regarding S-adenosylmethionine attenuation of acetaminophen hepatic toxicity. This paper explored protein carbonylation and 4-HNE adduction in hepatic tissue as well as mitochondrial and extramitochondrial samples. This paper was a collaborative effort with Dr. Serrine Lau at the University of Arizona. This paper is the first publication to identify 4-HNE adducted proteins associated with acetaminophen overdose and the specific amino acids adducted. This paper had 1 undergraduate from my laboratory as well as 2 graduate students from my lab and 2 from the U of Arizona. Coordination of this work demonstrates my ability to coordinate a study with individuals outside of our university.

a. Brown JM, Kuhlman C, Terneus MV, Labenski MT, Lamyaithong AB, Ball JG, Lau SS, Valentovic MA. S-adenosyl-l-methionine protection of acetaminophen mediated oxidative stress and identification of hepatic 4-hydroxynonenal protein adducts by mass spectrometry. Toxicol Appl Pharmacol. 2014 Dec 1;281(2):174-84.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/16KOhznM5cf58/bibliograpahy/47561182/public/?sort=date&direction=ascending

D. Research Support

ACTIVE

NASA Graduate WV Space Consortium Research Fellowship for Rachel Murphy $12,000 Valentovic M (PI). Grant Titled "Tenofovir Induced Nephrotoxicity, A Mechanistic Study" June 1, 2015- May 31, 2016.

COMPLETED

NIH R15CA161491-01A1 Dasgupta (PI) Valentovic (Co-Investigator) July 1, 2012 – June 30, 2015
PROJECT TITLE: **Capsaicin and Small cell Lung Cancer Therapy**
My primary responsibility wias to design, conduct and analyze the capsaicin pharmacokinetic studies in tumor bearing mice. Analysis has already been verified using HPLC with an electrochemical detector.

Marshall Health Translational Grant Program Valentovic (PI) Jan 1, 2013-January 31, 2015
Prenatal Exposure to Heavy Metals and Polycyclic Aromatic Hydrocarbons alter Umbilical Cord Blood Levels of thyroid Hormone and Vitamin D
Goal is to analyze human umbilical cord samples between urban and rural babies for metals and DNA-PAH adducts. We are also assessing Vitamin D status with RUCA zip codes to evaluate potential health risks between urban and rural births.

WV Rural Health Care Grant Valentovic (PI) January 1, 2013-Juy 31,2014
Urban and Rural Differences in Prenatal Exposure to Metals and Polycyclic Aromatic Hydrocarbons
Goal is to analyze human umbilical cord samples between urban and rural babies for metals and DNA=PAH adducts.

Funding Source: Flight Attendants Medical Research Association (FAMRA)
Title: Nicotine impact on lung cancer cells
Project Period: 07/01/2009 – 06/30/2014
Responsibility: Co-Investigator
Responsibility for experimental design and analysis of substances released by the lung in response to nicotine

3P20RR016477-09S4 Rankin (PI) September 24, 2009- Sept 24, 2012
West Virginia IDeA Network of Biomedical Research Excellence (WV-INBRE)
PROJECT TITLE for SUPPLEMENT: Mechanism of Resveratrol reduction of Cisplatin Renal Toxicity
ROLE: Project Director
Goal of this project is to characterize resveratrol attenuation of cisplatin renal toxicity. Further studies are exploring the cellular mechanism of resveratrol protection and reduction of oxidative stress mediated by cisplatin in the kidney.

PENDING

Funding Source: NIH R15 Dasgupta (PI) April 1, 2016 – March 30, 2019

Project Title: Capsaicin and Small cell Lung Cancer Therapy
Responsibility: Co-Investigator 5% effort. My role is to oversee and design the critical analyses of capsaicin derivatives in tissue, plasma and tumors. **Obtained an Impact Score of 20.**

Pharmaceutical Manufacturers Foundation Predoctoral Fellowship in Pharmacology and Toxicology June 1, 2016- May 31, 2018. Doctoral Student Rachel Murphy
Project Title: Examination of Mitochondrial Impairment and Oxidative Stress Mediated Renal Cytotoxicity by the Antiviral Agent Tenofovir.

Funding Source: NIH R21 Valentovic (co-PI with H. Yu) July 1, 2016- June 30, 2018
Project Title: Combined Inhalation of Rifaximin and tobramycin against "ESKAPE" pathogens.
Responsibility: Co-PI 15% time effort. Responsibility will be to design, direct and execute the pharmacokinetic studies with rifaximin including the development of the HPLC analysis of plasma and tissue samples. I will oversee the toxicology and safety studies for rifaximin.

Funding Source: NIH R15 PI: T. Salisbury July 1, 2016- June 30, 2019
PROJECT TITLE: Adipocyte/estrogenic regulation of leucine signaling in breast cancer.
Responsibility: Co-Investigator 5% effort. My role is to develop and oversee the quantitative measurement of leucine in samples isolated in the project. We will use HPLC analysis.