CURRICULUM VITAE

NAME: José E. Manautou

UNIV. ADDRESS: Dept. of Pharmaceutical Sciences, School of Pharmacy
69 North Eagleville Rd., Unit-3092
University of Connecticut
Storrs, CT 06269
phone: 860-486-3852
e-mail: jose.manautou@uconn.edu

HOME ADDRESS: 50 Elizabeth Lane, Vernon, CT 06066
Phone: 860-872-1554

EDUCATION:

1985: B.S. (Pharmacy), College of Pharmacy, Medical Sciences Campus, University of Puerto Rico.

1991: Ph.D. (Pharmacology and Toxicology), Dept. of Pharmacology and Toxicology, School of Pharmacy and Pharmacal Sciences
Purdue University
Advisor: Dr. Gary P. Carlson.

PROFESSIONAL EXPERIENCE:

1981-1982: Undergraduate Teaching Assistant, Biology Department, Cayey University College, University of Puerto Rico.

1983-1984: Undergraduate Research Training, Laboratory of Neurobiology, University of Puerto Rico. Advisor: Dr. Gladys Escalona.

1984: Purdue University AIM/MARC Summer Research Intern, Purdue University. Advisor: Dr. George K.W. Yim.

1984: Pharmacist Practitioner, Hospital del Maestro, San Juan, Puerto Rico.

1984-1985: Pharmacology and Toxicology Tutor, School of Pharmacy, University of Puerto Rico.

1985-1991:	Graduate Teaching Assistant in Undergraduate Pharmacology and Toxicology Laboratory, Purdue University.
1992-1994:	Postdoctoral Research Training, Center for Biochemical Toxicology, University of Connecticut. Advisor: Dr. Steven D. Cohen.
1995-2001:	Assistant Professor of Toxicology; Dept. Pharmaceutical Sciences, School of Pharmacy, University of Connecticut.
2001-present:	Associate Professor of Toxicology; Dept. Pharmaceutical Sciences, School of Pharmacy, University of Connecticut.
2003:	Sabbatical Leave; Amsterdam Liver Center, Academic Medical Center, University of Amsterdam, The Netherlands. Sponsor: Ronald Oude-Elferink

HONORS AND AWARDS:

1979-1985:	Scholarship from Government of Puerto Rico.
1980:	Dean's Honor Award; Cayey University College, University of Puerto Rico**.**
1980, 1984:	Who's Who Among the Students in American Universities and Colleges.
1980, 1983:	National Dean's List, University of Puerto Rico.
1983-1984:	Pharmacy School Delegate, Medical Science Campus General Student Council, University of Puerto Rico.
1984-1985:	Vice-President, Pharmacy School Student Council, University of Puerto Rico.
1985:	The Upjohn Company Award for Most Outstanding Academic Average and Leadership, College of Pharmacy, University of Puerto Rico.
1985:	Honors Graduate, College of Pharmacy, University of Puerto Rico.
1985-1986:	Department of Education Fellowship for Minority Students, Purdue University.
1985-1988:	The Patricia Roberts Harris Minority Fellowship, Purdue University.
1988:	Society of Toxicology Student Travel Award.

1988-1991:	U.S. Department of Education and Purdue University Ethnic and Minority Fellowship.
1990:	Procter and Gamble Student Travel Award to the American Society of Pharmacology and Experimental Therapeutics Meeting.
1990, 1991:	Albert and Anna Kienly Award for Excellence in Teaching by a Graduate Student, School of Pharmacy and Pharmacal Sciences, Purdue University.
1991:	Jenkins/Knevel Qualifying Graduate Student Research Award, School of Pharmacy and Pharmacal Sciences, Purdue University.
1992-1995:	NIEHS Postdoctoral Fellowship, University of Connecticut Institutional NRSA.
1993-1994:	American Liver Foundation Postdoctoral Research Fellowship.
1993:	National Science Foundation Travel Award to the NATO Advance Study Institute on "Molecular Aspects of Oxidative Drug Metabolizing Enzymes and their Significance in Environmental Toxicology, Chemical Carcinogenesis and Health" held in Kusadassi, Turkey.
1994:	Young Scientist Travel Award to the XIIth UPHAR Congress, Montreal, Canada.
1995:	Visiting Professor; University of Puerto Rico School of Pharmacy.
1996:	Keynote Speaker, Purdue University MARC/AIM Summer Research Program.
1998-2001:	Appointed Member, Placement Committee, Society of Toxicology Placement Committee Co-Director (1999-2000) Placement Committee Director (2000-2001)
1998-2001:	Appointed Member, Education Sub-Committee for Minority Programs, Society of Toxicology.
2001-2003:	Elected, Councilor, Mechanisms Specialty Section, Society of Toxicology
2001-2002:	Ad Hoc Member, Education Sub-Committee for Minority Programs, Society of Toxicology.
2002-2007:	Society of Toxicology, Assistant Coordinator for Minority Programs.

2007-present	Society of Toxicology, Coordinator for Minority Programs.
2002:	Member, NIH/NCI Special Emphasis Panel on Innovative Toxicology Models for Drug Evaluation.
2003-2005:	Elected, Councilor, Society of Toxicology
2003-2005:	Council Liaison, Specialty Sections (2003-2005)
2003-2005:	Council Liaison, Education Sub-Committee for Minority Programs (2003-2005)
2004-2005:	Member, Council Subcommittee on Contemporary Concepts in Toxicology and Non-SOT Meetings (2004-2005).
2004-2005:	Council Co-Liaison, NIH Funding Task Force (2004-2005).
2004-2005:	Council Liaison and Chair, Special Interest Group Task Force
2004-2006:	Member, The Toxicology Education Foundation (TEF) Steering Team for the "Is It Safe?" project.
2005-2006:	Chair, Society of Toxicology Special Interest Groups Task Force
2006-2007	Member, Society of Toxicology Member Services Strategy Committee
2005-2006	Member, National Research Council Committee on Human Health Risks of Trichloroethylene.
2005:	External Evaluator, European Commission Sixth Framework Programme on Food Quality and Safety. Specific Target Research Project (STREP) T5.4.8.4: Risk Assessment of Non-Dioxin-Like Polychlorinated Biphenyls. Brussels, Belgium.
2006-2009:	Reviewer, NIH XNDA Study Section.
2006-2007	Member, Society of Toxicology Member Services Strategy Committee
2006	Achievement Award, Society of Toxicology
2007	External Reviewer: US EPA Toxicological Review fort he Bromobenzene Human Health Assessment
2007	2007 Committee on Institutional Cooperation (CIC) Summer Research Opportunity Program (SROP) Alumni Award, Purdue University.
2007-2010	Cohen Marlene L. Cohen and Jerome H. Fleisch Scholar

2008:	Society of Toxicology AstraZeneca Traveling Lectureship Award
2007-present:	Fellow, Academy of Toxicological Sciences
2009:	Stewardship Award on the 20th Anniversary of the Minority Undergraduate Program of the Society of Toxicology
2009:	Member, NIH ZRG1 DKUS F-96 Special Emphasis Panel
2009-present:	Elected Member, Board of Directors of Academy of Toxicological Sciences.
2010:	Member, EPA Science Advisory Board (SAB) Trichloroethylene Health Assessment Review Panel
2010-2012:	Member, NIH College of CSR Reviewers
2009:	Society of Toxicology Mechanisms Specialty Section, Vice President-Elect
2010:	Society of Toxicology Mechanisms Specialty Section, Vice President
2011:	Society of Toxicology Mechanisms Specialty Section, President
2010-2012:	Society of Toxicology Communications Task Force
2010-2012:	Elected Member, Society of Toxicology Specialty Sections Governance Group
2010-present:	Member, EPA, Human Studies Review Board
2010-2011:	Member, Steering Committee, 2011 Gordon Research Conference on Cellular and Molecular Mechanisms of Toxicity: Understanding Innovative Mechanistic Toxicology in the Post-Genomic Era.
2010:	NIEHS Board of Scientific Counselors (membership nomination undergoing vetting process).
2010:	9th International ISSX Meeting Abstract Review Committee.

EDITORIAL APPOINTMENTS, PEER REVIEW

1997-2003:	Member, Alumni Advisory Board, Institute for Diversity in Biomedical Science, Purdue University.
1997-2005:	Member, Editorial Board, *Journal of Toxicology and Environmental Health*.
1996-present:	Member, Medical Advisory Committee, Connecticut Poison Control Center.

2001-2006: Member, Editorial Board, *Toxicology and Applied Pharmacology*.

2006-present: Member, Editorial Board, *Toxicological Sciences.*

2006-present: Associate Editor, *Toxicology and Applied Pharmacology*

2007-present: Member, Editorial Board, *Toxicology in Vitro*

2007-2010: Member, Editorial Board, *Liver International*

2008-present: Member, Editorial Board, *Toxicology*

2009-2013: Member, Editorial Board, *World Journal of Gastrointestinal Pathophysiology*

2009-present: Member, Editorial Board, *Drug Metabolism Reviews*

Ad hoc reviewer for: *Journal of Toxicology and Environmental Health, Toxicology, Biochemical Pharmacology, Drug Metabolism and Disposition, Toxicological Sciences, Life Sciences, Toxicology and Applied Pharmacology, Toxicology Letters, Journal of Pharmacology and Experimental Therapeutics, Environmental Health Perspectives, Journal of Hepatology, Journal of Pharmacy and Pharmacology, Proteonomics, Hepatology, Cell Stress & Chaperones, Molecular Pharmacology, Food and Chemical Toxicology, Chemico-Biological Interactions, Chemical Research In Toxicology.*

EXTERNAL PROMOTION TENURE AND RE-APPOINTMENT REVIEWS

2007: Department of Pharmacology and Toxicology, University of Arizona College of Pharmacy

2009: Department of Pharmacology, Toxicology and Therapeutics at the University of Kansas School of Medicine

2010: Department of Pharmaceutical Sciences, University of Colorado, Denver

2010: Department of Pathology and Laboratory Medicine, University of California, Irvine

MEDIA (TV INTERVIEWS & PRINTED MEDIA)

2006	Interview for NBC30 News on dangers of excessive use of over-the-couter medications containing acetaminophen. Aired on December 20, 2006.
2009	Hispanic Information and Telecommunications Network, Inc. (HITN). Appearance in TV program *"Dialogo de Costa a Costa"* to discuss intentional and non-intentional poisoning in children in the United States. Aired on March 17, 2009.
2010	Interview for the Hispanic Outlook magazine for higher education on the 9th Annual Biochemical Research Conference for Minority Students (ABRCMS). June 7, 2010 issue.

UNIVERSITY AND SCHOOL ACTIVITIES AND COMMITTEES

1995-1996:	Member, School of Pharmacy Animal Care and Laboratory Safety Committee.
1995-present:	Faculty Advisor, Academy of Students of Pharmacy (APhA-ASP).
1997-1999:	Member, Search Committee, Vice Provost for Multicultural Affairs, University of Connecticut.
1995-1997:	Coordinator, Summer Research Program in Toxicology for Minority Students.
1997-present:	Toxicology Scholars Colloquium Steering Committee, Chair.
1998-1999:	Member, School of Pharmacy Seminars Committee.
1998-present:	Faculty Associate, University of Connecticut Institute for Puerto Rican and Latino Studies.
1998:	Member, Neag School of Education Ad Hoc Committee on Bilingual Education.
1998:	Member, Dean's Task Force on Satisfaction with Courses, Advising and Career Counseling.
1999-2000:	Faculty Secretary, Department of Pharmaceutical Sciences.
2000-2008:	Advisory Board, University of Connecticut Center for Academic Programs.

2000-present:	Member, Edward A. Khairallah Memorial Fund Advisory Committee
2001-2002:	University of Connecticut Diversity Task Force.
2001-2003:	Dean's Advisory Council on Promotion, Tenure and Reappointment. Chairperson, 2002-2003.
2002-present:	Member, School of Pharmacy Program Assessment Committee.
2004:	Member, Search Committee, Director of the Puerto Rican and Latin American Cultural Center.
2005:	Member, Search Committee, Pfizer Endowed Chair in Pharmaceutical Technology.
2005:	Member, ACPE Self-Study, Students Committee
2006:	Chair, Search Committee, Boehringer Ingelheim Endowed Chair in Mechanistic Toxicology
2006-present:	Faculty Representative to the School of Pharmacy Advisory Board Meeting.
2007:	Member, Review Committee Dean of the School of Pharmacy
2008-present:	Member, Member, University of Connecticut Centers and Institutes Review Committee
2009-present:	Pharmacology and Toxicology Graduate Program Coordinator.
2010-2011:	Chair, University of Connecticut Centers and Institutes Review Committee

PROFESSIONAL AFFILIATIONS:

1993-present:	Member, North East Chapter of Society of Toxicology Councilor: 1996-1998
1995-present:	Member, International Society for the Study of Xenobiotics
1996-present:	Member, Society of Toxicology
1996-present:	Member, American Association of Colleges of Pharmacy
1996-present:	Member, American Pharmaceutical Association

1996-present:	Member, Kappa Psi Pharmaceutical Fraternity
1997-present:	Member, American Association for the Advancement of Science
2000-present:	Member, Rho Chi Pharmacy Honor Society
2007-present:	Member, American Society for Pharmacology and Experimental Therapeutics
2007-present	Member, International Association for the Study of the Liver
2010-present	Member, Phi Lambda Sigma Pharmacy Leadership Society

INVITED PRESENTATIONS OF SEMINARS, LECTURES AND PANEL DISCUSSIONS:

1995:	Society of Toxicology Educational Program for Minority Students: "Panel Discussion of Graduate School and Career Experiences", Baltimore, MA.
1995:	University of Puerto Rico, Center for Environmental Research and Toxicology, School of Pharmacy: "Clofibrate: Protection Against Acetaminophen Hepatotoxicity", San Juan, PR.
1995:	University of Puerto Rico School of Pharmacy, Center for Environmental Research and Toxicology, School of Pharmacy: "Biochemical Alterations and Mechanisms of Carcinogenesis by Peroxisome Proliferators", San Juan, PR.
1996:	Society of Toxicology Undergraduate Educational Program: "Discussion of Graduate School and Career Experiences", Anaheim, CA.
1996:	University of Connecticut, Dept. of Pathobiology: "Peroxisome Proliferators: Modulators of the Actions of Hepatotoxic Agents", Storrs, CT.
1997:	Meharry Medical College, Depts. of Pharmacology and Family and Preventive Medicine: "Peroxisome Proliferators: Modulators of Susceptibility to the Action of Hepatotoxic Agents", Nashville, TN.
1997:	Society of Toxicology Annual Meeting Undergraduate Educational Program: "Mentors and Mentoring in the Discipline of Toxicology", Cincinnati, OH.
1977:	Zeneca Pharmaceuticals, Drug Disposition and Metabolism Department: "Possible Mechanisms of Protection Against the Action of Model Hepatotoxic Agents by Treatment with the Hypolipidemic Drug Clofibrate", Wilmington, DE.

1998: Northeastern University, Dept. of Toxicology: “Pretreatment with Clofibrate Diminishes the Action of Hepatotoxic Compounds: Mechanistic Investigation”, Boston, MA.

1998: Mount Holyoke College: “Exploring Opportunities in Diverse Science Research”, South Hadley, MA.

1999: Society of Toxicology Meeting: “Basic Concepts on Chemically-Induced Liver Injury”, New Orleans, LA.

1999: NIH Summer Research Institute for Diversity in Biomedical Sciences, Dinner Speaker: “Experiences in Graduate Education, Research and Academia”, Purdue University, W. Lafayette, IN.

1999: Astra-Zeneca, Drug Disposition and Metabolism Department: “Hepatoprotection by Peroxisome Proliferators: Role of ATP-dependant Transport Proteins”, Wilmington, DE.

2000: Society of Toxicology Meeting: “Basic Concepts on Chemically-Induced Liver Injury”, Philadelphia, PA.

2003: APhA-ASP Mid-Year Regional Meeting: “Enhancing your PharmD Workshop”. Providence, RI.

2004: Boehringer Ingelheim Pharmaceuticals, Inc.: “Hepatic Detoxification and Disposition Mechanisms, Peroxisome Proliferators and Biliary Excretion/Hepatic Transport Proteins in Acetaminophen Hepatotoxicity” Ridgefield, CT.

2004: Society of Toxicology Meeting, Placement Workshop: “Taking Command of you Career – Keeping Skills Up to Date”, Baltimore, MD

2004: V Congreso Mexicano de Toxicologia: “Conceptos Basicos de Daño Hepatico Producido por Quimicos y el Efecto de Proliferadores de Peroxisomas en Toxicidad por Acetaminofen”, Guadalajara, Mexico.

2004: Northeastern University, School of Pharmacy: “Multidrug-resistance proteins and their role in the hepatobiliary disposition of acetaminophen”, Boston, MA.

2004: Boehringer Ingelheim Pharmaceuticals, Inc: “Hepatobiliary Disposition of Acetaminophen in Animal Models Lacking Multidrug Resistance Proteins 2 and 3”, Ridgefield, CT.

2004: Korean Society of Toxicology: “Prevention of Acetaminophen Hepatotoxicity by the Hypolipidemic Drug Clofibrate: Mechanistic Studies", Seoul National University, Seoul, South Korea.

2004: University of Connecticut Health Center Pharmacogenetics Research Network & Knowledge Base Network: "Acetaminophen Liver Injury, Hepatobiliary Disposition and Regulation of Multidrug Resistance Proteins", Farmington, CT.

2005: Massachusetts College of Pharmacy and Health Sciences: "Hepatic Acetaminophen Excretion via Multidrug Resistance Proteins", Worcester, MA.

2005: INBRE Seminar Series, University of Rhode Island: "Altered Hepatobiliary Disposition of Acetaminophen in Animal Models Lacking Multidrug-Resistance Proteins", Kingstone, RI.

2005: NEF-The African Education Initiative Toxicology and Pathology Lecture Series: "Introduction to Drug-Induced Liver Disease". Ahmadu Bello University, Zaria, Nigeria.

2005: Eli Lilly and Company, "Hepatobiliary Disposition of Acetaminophen and Regulation of Multidrug Resistance Transport Proteins in Response to Chemical Liver Injury", Indianapolis, IN.

2006: Curriculum in Toxicology, University of North Carolina: "Hepatic Transporters and Acetaminophen: Implications in Drug Disposition and Hepatotoxicity", Chapel Hill, NC.

2006: Penn State University, Center for Molecular Toxicology and Carcinogenesis, "Peroxisome Proliferation and Resistance to Drug-Induced Liver Disease", University Park, PA

2006: University of Puerto Rico, School of Medicine: "Hepatic Transport Mechanisms and Xenobiotic Disposition". San Juan, Puerto Rico.

2006: 14th North American ISSX Meeting: "Efflux Transporters: Important Determinant of Drug-Induced Liver Injury", Rio Grande, Puerto Rico

2006: 3rd Annual Meeting of the North American Hepatocyte Research Association: "Changes in Liver Transport Protein Expression as an Adaptive Response to Drug-Induced Hepatotoxicity", Rio Grande, Puerto Rico

2006: 23rd Annual NUTMEG Meeting: "Hepatobiliary Disposition of Acetaminophen and its Metabolites in Transport Deficient Animal Models" Sturbridge, MA.

2006: Rutgers University Environmental and Occupational Health Sciences Institute (EOHSI): "Transcriptional Regulation of Multidrug Resistance Efflux Transporters During Acetaminophen Hepatotoxicity". Piscataway, NJ

2007: Bristol Myers Squibb: "Drug-Induced Liver Injury Elicits Compensatory Changes in Hepatobiliary Transporters". Princeton, NJ.

2007: McNeil Consumer Healthcare: "Acetaminophen and Drug Transporters: Implications to Toxicity", Fort Washington, PA.

2007: Department of Pharmacology and Toxicology, Michigan State University: "Changes in Expression of Hepatobiliary Transport Proteins as a Compensatory Response to Drug-Induced Hepatotoxicity", East Lansing, MI

2007: 2007 AAPS Workshop on Drug Transport in ADME: From the Bench to the Bedside, "Expression of Drug Transporters in Mouse and Human Liver During Acetaminophen Hepatotoxicity", Bethesda, MA.

2007: 2007 African Education Initiative International Scientific Conference: Integrating New Technologies in Drug Development, "Drug-Induced Hepatotoxicity", Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

2007: 2007 African Education Initiative International Scientific Conference: Integrating New Technologies in Drug Development, "Role of Multidrug Resistance Proteins in the Hepatobiliary Disposition of Xenobiotics", Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

2007: 2007 Gordon Research Conference in Drug Metabolism: "Transcriptional and Signaling Mechanisms Regulating Drug Transporters in Drug-Induced Hepatotoxicity", Holderness School, Plymouth, NH

2007: 2007 CIC/SROP Conference: "Workshop on Careers in Industry, Government and Academia", Purdue University, West Lafayette, IN.

2007: 10th Annual Land O'Lakes Conference on Drug Metabolism/Applied Pharmacokinetics: "Hepatic Transporters: Metabolism/Safety", Devil's Head Resort, Merrimac, WI.

2007: Nova Southeastern University School of Pharmacy – Ponce, Puerto Rico: White Coat Ceremony Keynote Speaker.

2007: Seoul National University School of Pharmacy: "Multidrug Resistance-Associated Protein 4: Determinant of Tolerance Development to Acetaminophen Hepatotoxicity", Seoul, South Korea.

2007: Yale University School of Medicine, Section of Digestive Diseases: Oxidative Stress and Kupffer Cell Function Mediate the Changes in Liver Transport Protein Expression by Produced by Toxic Exposure to Acetaminophen", New Heaven, CT.

2007: Delaware Valley Drug Metabolism Discussion Group: "Characterization of Transporters Expression in Liver Following Toxic Acetaminophen Exposure", Plymouth Meeting, PA.

2008: University of Utah, Dept. of Pharmacology and Toxicology: "Induction of Multidrug Resistance Proteins by Toxic Acetaminophen Exposure: Potential Role on Development of Tolerance to Hepatotoxicity", Salt Lake City, Utah. *<u>*External seminar speaker selected by the graduate students in the program**</u>.

2008: Indiana University Medical School, Department of Pharmacology and Toxicology: "Hepatobiliary Transport Proteins are Regulated by Kupffer Cell-and Nrf2-Related Signaling Pathways During Acetaminophen-Induced Hepatotoxicity", Indianapolis, IN.

2008: Texas A&M University, The Interdisciplinary Faculty of Toxicology: "Regulation of Hepatic Drug Transporter MRP4/ABCC4 during Drug-Induced Liver Injury". College Station, TX.

2008: Cambridge Healthtech Institute's Seventh Annual World Pharmaceutical Congress: "Characterization of Liver Multidrug Resistance Protein 4 (Mrp4) Expression During Acetaminophen Hepatotoxicity", Philadelphia, PA.

2008: Hoffmann-La Roche, Inc.: "Analysis of Gene Expression and Regulation of Hepatic Drug Transporters in Response to Acetaminophen Hepatotoxicity", Nutley, NY

2008: AstraZeneca R&D Headquarters: "Characterization of Mrp4 (Abcc4) Regulation in Response to Acetaminophen (Paracetamol) Hepatotoxicity", Sodertalje, Sweden; Sept. 1, 2008.

2008: Center for Xenobiotic and Environmental Risk Research (XERR), University of Zurich, University of Basel, Eawag Dübendorf : "Regulation of hepatobiliar transporters in a mouse model of acetaminophene (paracetamol) autoprotection ", Zurich, Switzerland; Sept. 4, 2008.

2008: Solvo Biotechnology: "Compensatory Increase in hepatic Mrp4 Expression by Toxic Paracetamol Treatment: Does it Influence Susceptibility to Hepatotoxicity Upon Paracetamol Re-Exposure?", Budaörs, Hungary; Sept. 10, 2008.

2008: Centre d'Immunologie de Marseille Luminy: "Peroxisomes Proliferators Prevent Hepatotoxicity by Paracetamol: Mechanistic Investigation and Potential Role for Vanin-1 Induction", Marseille, France; Nov. 17, 2008.

2008: University of Coimbra, Center for Neurosciences and Cell Biology, Department of Zoology: "Compensatory Increase in Hepatic Mrp4 Expression by Toxic

Paracetamol Treatment: Does it Influence Susceptibility Upon Paracetamol Re-Exposure?", Coimbra, Portugal; November, Nov. 21, 2008.

2008: AstraZeneca UK: "Multidrug Resistance-Associated Protein 4 (Mrp4; Abcc4): Determinant of Tolerance to Acetaminophen (Paracetamol) Toxicity?", Alderley Park, England; November 25, 2008.

2008: Hoffmann-La Roche, Inc.: "Analysis of Gene Expression and Regulation of Hepatic Drug Transporters in Response to Acetaminophen Hepatotoxicity". Nutley, NJ; Dec. 9, 2008.

2009: The University of Arizona College of Pharmacy: "Role of Mrp4 in Acetaminophen-Induced Hepatotoxicity", Tucson, AZ; February 11, 2009.

2009: SOT Undergraduate Education Program: "Introduction to Toxicology" SOT 48th Annual Meeting, Baltimore MA; March 15, 2009.

2009: Massachusetts College of Pharmacy and Health Sciences, Worcester/Manchester, Rho Chi Society Gamma Pi Chapter Induction Ceremony Keynote Speaker, Worcester, MA; April 16, 2009.

2009: National Institute of Environmental Health Sciences, Laboratories of Pharmacology and Molecular Toxicology: "Compensatory Responses to Xenobiotic-Induced Liver Injury: How Important is the Induction of Multidrug Resistance Protein 4 (MRP4; ABCC4)?" Research Triangle Park, NC; May 14, 2009.

2009: Auburn University School of Pharmacy: "Changes in Liver Multidrug Resistance Associated Protein-4 (Mrp4) Expression and its Potential Implications to Drug Hepatotoxicity", Auburn, AL; Sept. 22, 2009.

2009: 16th North American Regional ISSX Meeting, Short Course 1 - Transporters in Drug Disposition and Elimination: "Function and Regulation of Basolateral and Canalicular Liver Transporters", Baltimore, MD; October 18, 2009.

2009: Annual Biomedical Research Conference for Minority Students (ABRCMS), "Liver Drug Transporters and Their Contributions to Drug-Induced Hepatotoxicity", Phoenix, AZ; November 5, 2010. *Sponsored by the Society of Toxicology*

2009: Carole and Ray Neag Comprehensive Cancer Center Sixth Annual Research Retreat: "ABC Transporters: A Role Beyond Multidrug Resistance", Farmington, CT; November 13, 2009.

2009: University of Connecticut, Department of Nutritional Sciences: "Importance of Hepatic Multidrug Resistance Proteins During Drug-Induced Hepatotoxicity", Storrs, CT; November 21, 2009.

2010: 49th Annual Meeting of the Society of Toxicology: "Mechanistic Role of Reactive Intermediate Covalent Binding in Target Organ Toxicity: Past, Present and Future", Symposium Chair, Salt Lake City, UT; March 8, 2010.

2010: 49th Annual Meeting of the Society of Toxicology: "Understanding the Cross-Talk Between Bile Salt Export Pump (BSEP) and Other Efflux Transporters in the Manifestation of Drug-Induced Liver Injury", Salt Lake City, UT; March 9, 2010.

2010: Ninth Annual World Pharmaceutical Congress, CE Course on Mechanistic Insights into Hepatotoxicity, "Inhibition of Bile Acid Efflux Protein and Involvement of Hepatic Transporters in Drug-Induced Hepatotoxicity", Philadelphia, PA; June 16, 2010.

2010: Ninth Annual World Pharmaceutical Congress, Unraveling Mechanisms Underlying Hepatotoxicity Symposium, "Transcriptional and Signaling Regulation of ABCC Genes by Hepatotoxicant Treatment", Philadelphia, PA, June 17, 2010

2010: XII International Congress of Toxicology: "Present and Future Challenges in Safety Assessment for Pharmaceuticals in Iberoamerica", Barcelona, Spain, July, 22, 2010

2010: 9th International Meeting of the International Society for Studies in Xenobiotics "Regulation of Drug Transporters in Different Disease States and its Toxicological and Clinical Implications", Istanbul, Turkey, September 5, 2010

2010: Asociación Toxicológica Argentina, XXVIII Jornadas Interdisciplinarias de Toxicologia, "Mecanismos de Regulación de Proteínas de Transporte en Hígado a Consecuencia de Daño Hepático Agudo por Acetaminofen", Buenos Aires, Argentina, September 22, 2010.

GRANTS

1995-1998: University of Connecticut Offices of the Chancellor and Dean of the School of Pharmacy, "Summer Research Program in Toxicology for Minority Undergraduate Students", $21,000.

1996-1997: University of Connecticut Research Foundation: "Alterations in the Expression of ATP-dependent Transport Proteins in Biliary Canaliculi by Peroxisome Proliferators and its Association with Resistance Against the Action of Model Hepatotoxic Agents", J. Manautou (P.I.), $10,000.

1998-2000: Pharmaceutical Research and Manufacturers of America Foundation: "Regulation of Hepatic ATP-dependent Transport Proteins and their Potential Role in the Hepatobiliary Secretion of Model Hepatotoxic Agents", J. Manautou (P.I.), $25,000.

1998-2001: AstraZeneca, Phase III Metabolism: "Biliary Canalicular ATP-dependent Transport Proteins and their Role in Xenobiotic Disposition", J. Manautou (P.I.), $98,750.

2000-2003: NIH R-15: "Analysis of MRP-2 (cMOAT) Expression During Hepatocellular Proliferation", J. Manautou (P.I.), $106,876.

2002-2003: University Of Connecticut Research Foundation: "Changes in Susceptibility to Acetaminophen Hepatotoxicity by Treatment with Model Organic Anions", J. Manautou (P.I.), $11,680

2002-2003: Pfizer, Inc: "Effect of CP-419,342-01 on Canalicular Membrane Vesicle Transport and Protein Function", J. Manautou (P.I.), $22,800.

2003: Pharmaceutical Research and Manufacturers of America Foundation (PhRMA) Sabbatical Fellowship in Pharmacology and Toxicology: "Hepatic Transport of Acetaminophen and its Metabolites: *In Vitro* Analysis", J. Manautou (P.I.), $40,000.

2003-2008: Howard Hughes Medical Institute: "Regulation of Hepatic Multidrug Resistance Protein 3 (Mrp3) During Oxidative Stress." Predoctoral Fellowship in Biomedical Sciences to graduate student Lauren Aleskunes, $185,000.

2005-2006: University of Connecticut Research Foundation: "Regulation of Transporter Expression by Nrf2 during Drug-Induced liver Injury", J. Manautou (P.I.), $6,400.

2005-2009: NIH 1R01 DK069557-01 "Transporter Expression in Response to Hepatotoxicants", J. Manautou (P.I.), $1,044,141.

2005-2006: Pfizer, Inc: "Expression of Murine and Human Hepatic Transport Proteins During Drug-Induced Liver Injury", J. Manautou (P.I.), $22,000.

2005-2009 :NIH PA03-026 "Minority Programs for the Society of Toxicology Meeting, J. Manautou (P.I.), $302,881.

2005-2006 Environmental Protection Agency "Undergraduate Education Program for the 2006 Society of Toxicology Annual Meeting", J. Manautou (P.I.), $25,000.

2006-2008 Pharmaceutical Research and Manufacturers of America Foundation (PhRMA). "Regulation of Hepatic Transporter Expression by Inflammatory Mediators During Drug-Induced Liver Injury". Predoctoral Fellowship in Pharmacology and Toxicology for Sarah Barnes, $40,000.

2009-2010 Recovery Act Administrative Supplement to DK069557 "Transporter Expression in Response to Hepatotoxicants" J. Manautou (P.I.), $99,999 (awarded).

2009-2010 3T36GM008397-16S1 Minority Program for Society of Toxicology Meeting, J. Manautou (P.I.), $5,659

2009-2011 NIH 1RC1DK086879-01 "Drug Transporters, Kupffer Cells and Acetaminophen Hepatotoxicity" J. Manautou (P.I.), $574,664 (pending).

2005-2009 2R01 DK069557-05 "Transporter Expression in Response to Hepatotoxicants", J. Manautou (P.I.), $1,880,497 (Study Section review completed on June 16; Impact/Priority Score: 24; Percentile: 9).

SUMMARY OF RESEARCH ACCOMPLISHED AND AREAS OF RESEARCH INTEREST:

Dr. Manautou's research interests are on biochemical and genetic determinants of susceptibility to the action of hepatotoxicants. His laboratory has carried out a comprehensive characterization of the expression of multiple uptake and efflux drug transporters in mice following acetaminophen and carbon tetrachloride exposure. His studies have shown that hepatotoxic doses of these chemicals decrease mRNA and protein levels of uptake drug transporters, while increasing the levels of efflux transporters such as the multidrug resistance-associated family of proteins (Mrp proteins). Zonal analysis of protein expression demonstrates induction of Mrp isoforms 3 and 4 in centrilobular hepatocytes. Furthermore, immunochemical staining is localized to cells undergoing active replication adjacent to injured zones. Mrp3 and 4 are efflux transporters located in the basolateral membrane of hepatocytes and they mediate the elimination of endogenous compounds and xenobiotics into sinusoidal blood. Subsequent administration of a second, higher dose of acetaminophen to mice results in lower hepatotoxicity, a phenomenon known as autoprotection. Interestingly, this autoprotection is seen in association with a much more robust induction in Mrp4 expression. From these studies Dr. Manautou has hypothesized that up-regulation of efflux transporters, particularly Mrp4, is a protective mechanism that minimizes accumulation of potentially toxic chemicals in hepatocytes and may also be a mechanism for enhanced paracrine signaling within the liver during recovery from injury. His group now investigates regulatory factors underlying the changes in transport protein expression induced by hepatotoxicant treatment of mice. The focus has been on the transcription factor nuclear factor E2-related factor 2 (Nrf2) and on signaling molecules originating from Kupffer cells. Nrf2 is activated during periods of oxidative stress and is responsible for the transcriptional regulation of multiple antioxidant and detoxification genes, while Kupffer

cell function is known to influence the susceptibility of the liver to toxicants. Studies with Nrf2 knockout mice demonstrate that the up-regulation of Mrp3 and Mrp4 by APAP is dependent on Nrf2 expression. Similarly, mice depleted of Kupffer cell function show an impaired capacity to increase expression of some Mrp proteins in response APAP treatment. Collectively, these studies provide insightful information on the regulation of hepatobiliary transporters expression in mice during drug-induced liver injury. Similar changes in transport protein expression were seen in liver specimens from individuals with acute APAP liver failure. Dr. Manautou also studies the mechanistic basis of protection against APAP hepatotoxicity by repeated dosing with the peroxisome proliferators cofibrate. His previous studies examined changes in selective APAP covalent binding, expression of target proteins, glutathione levels and activity of detoxifying and antioxidant pathways. More recently, Dr. Manautou's group employed a genomic approach to identify changes in gene expression that might be mechanistically relevant to the protection afforded by clofibrate. His group is currently pursuing some of the 53 "genes of interest" generated by gene array analysis. One of these genes is vanin-1. Dr. Manautou has proposed that vanin-1 is important for the protection against APAP hepatotoxicity afforded by clofibrate treatment since this protein is involved in the synthesis of cysteamine and cystamine. These are potent antioxidants known to prevent APAP hepatotoxicity in rodents and humans. His studies also showed that clofibrate-mediated induction of vanin-1 gene expression is dependent upon activation of the peroxisome proliferator activated receptor-alpha (PPARα). This is the key transcription factor that mediates multiple responses of the liver to peroxisome proliferators.

PAST GRADUTE TRAINEES:

Chuan Chen, Ph.D. (2001); current position: scientist at Arena Pharmaceuticals, San Diego, CA.

Gayle Hennig, Ph.D. (2002); current position: research associate, CTBR, Montreal, Canada.

Vanessa M. Silva, Ph.D. (2002); current position: scientist/toxicologist, Product Safety and Regulatory Affairs, Procter and Gamble, Cincinnati, OH.

Jeffery Moffit, Ph.D. (2006); current position: scientist/toxicologist at Boehringer Ingelheim Pharmaceuticals.

Lauren Aleksunes, Pharm.D., Ph.D. (2006); current position: Assistant Professor of Pharmacology and Toxicology, Rutgers University, Ernest Mario School of Pharmacy.

Sarah Campion, Ph.D. (2008); current position: scientists/toxicologists, Pfizer, Inc.

Meeghan O'Connor, M.S. (2010). current position: research assistant at St. Francis Hospital

PAST UNDERGRADUATE RESEARCH TRAINEES:

Kim Nguyen (Honors Graduate), B.S. in Pharmacy; current position: Registered Pharmacist. - *first author of a research article*

John Carbone, B.S. in Biology; M.D., University of Connecticut. - *co-author of a research article*

Vanessa M. Silva, B.S. in Pharmacy, University of Puerto Rico – *co - author of research article*

Elizabeth Peterson (University Scholar), B.S. in Environmental Health, Ph.D., Brown University; current position: Postdoctoral fellow, Yale University.

Lauren Aleksunes (University Scholar), Pharm.D. Ph.D.; current position: Assistant Professor of Pharmacology and Toxicology, Rutgers University, Ernest Mario School of Pharmacy.

Rachel Sykes, Pharm.D.

Michael Kardas, Pharm.D. - *co-author of a research article*

Marcy Blake-Kinnin, B.S., Molecular and Cell Biology

Jennifer Morrone, Pharm.D. - *co-author of a research article*

Michael Nowicki, Pharm.D. candidate - *first author of a research article*

NEA UCONN SUMMER PROGRAM INTERNS:

2007: Cristina Tatis – University Metropolitana de Puerto Rico

2008: Cristina Tatis – University Metropolitana de Puerto Rico – *co-author of a research article*

2009: Jaime J. Ramos – University of Puerto Rico, Aguadilla.

2010: Katirina Flores - University of Puerto Rico, Mayaguez

CURRENT GRADUATE STUDENTS:

Renato Scialis, B.S.

Meeghan O'Connor, B.S.

Daniel Ferreira, B.S.

Swetha Rudraiah, D.V.M.

CURRENT POSTDOCTORAL FELLOWS:

Xinsheng Gu, Ph.D., Texas A&M University

RESEARCH PUBLICATIONS; Ph.D. DISSERTATION:

Pulmonary Ethanol Metabolism (1991).

RESEARCH PUBLICATIONS; ABSTRACTS:

1. **Manautou, J.E.**, Kuta, C.C., and Yim, G.K.W (1984). Effect of chronic stress on gallstone formation in mice. Presented at AIM/MARC Summer Research Program, Purdue University and also presented at Industrial Pharmacist Committee and Puerto Rico Discussion Group, Scientific Session. Dorado, Puerto Rico.

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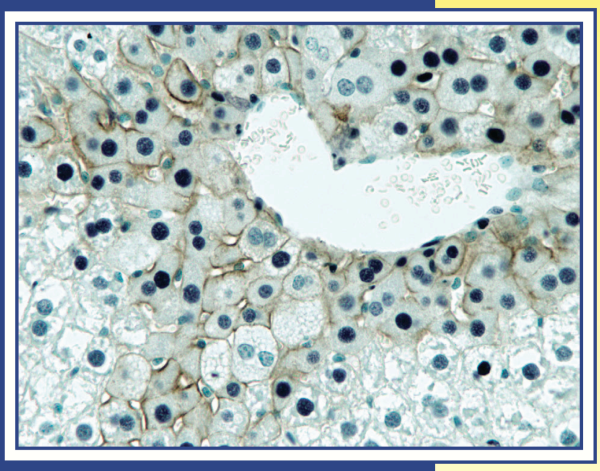

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DESCRIPTION OF RESEARCH AND FUTURE PLANS

A. Acetaminophen toxicity and hepatobiliary transporters

Acetaminophen (APAP), a commonly used over the counter analgesic and antipyretic agent, is responsible for 50% of all cases of drug-induced liver injury in the United States. Although APAP is possibly the most widely studied hepatotoxic drug, many questions remain unanswered about its mode of toxicant action. *The popularity of this drug, along with its potential for drug-related morbidity and mortality makes it a significant human health problem.* Even less is known about the development tolerance to APAP toxicity that has been documented in laboratory animals and the clinic. Pre-exposure to supra-therapeutic doses of APAP or incremental APAP dosing is known to lead to resistance to doses that would otherwise produce substantial toxicity. The central hypothesis of our research work during the last 5-6 years is that changes in expression of hepatobiliary transporters contribute to the development of tolerance to APAP hepatotoxicity.

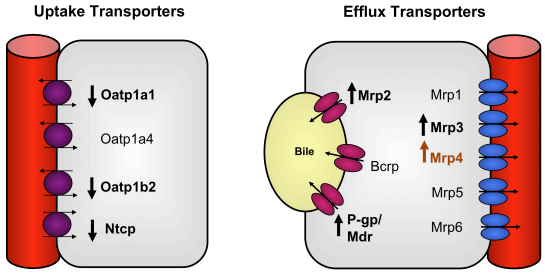

Figure 1. Changes in expression of liver transporters by APAP and CCl_4. *Both toxicants produce very similar changes in transporter protein expression; induction of efflux transporters and reduction in uptake transporters expression. Mrp4 was the most significantly induced transporter by both toxicants (highlighted in different font color). Maximal changes in protein expression were seen at 48 hr after treatment (APAP, 400 mg/kg; CCl4, 10 ul/kg).*

In order to address this, we have conducted an extensive zonal and temporal characterization of changes in expression of both efflux and uptake liver transporters in response to toxic APAP treatment. First, we showed that several multi-drug resistance associated proteins (Mrps) are significantly induced, while members of the organic anion transporter polypeptide (Oatp) family of uptake transporters are down-regulated during APAP liver injury in mice. Mrp4 is the most significantly induced transporter (16-fold induction at 48 hr after APAP treatment). Figure 1 illustrates the changes in transporter protein expression by APAP and carbon tetrachloride (CCl_4). The latter was included in our analysis as a hepatotoxicant with different mechanistic features and as a chemical whose entry and efflux from the liver is transporter-independent.

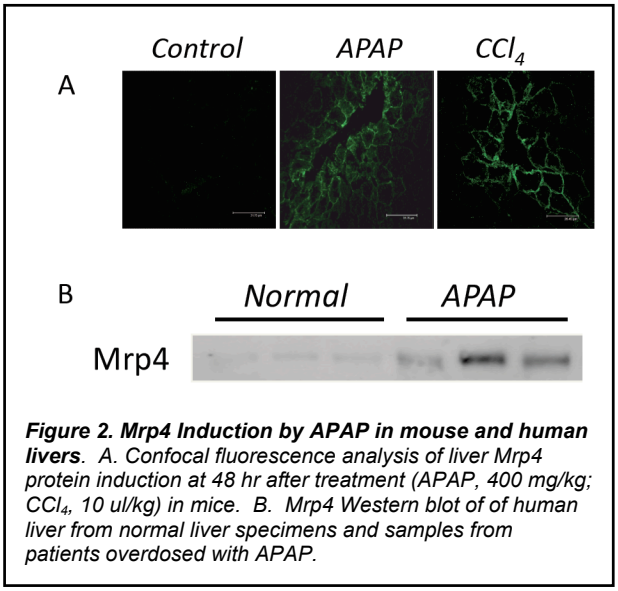

Figure 2. Mrp4 Induction by APAP in mouse and human livers. *A. Confocal fluorescence analysis of liver Mrp4 protein induction at 48 hr after treatment (APAP, 400 mg/kg; CCl_4, 10 ul/kg) in mice. B. Mrp4 Western blot of of human liver from normal liver specimens and samples from patients overdosed with APAP.*

The relevance of these findings to human acetaminophen toxicity was demonstrated in studies where human liver samples from patients that overdosed with APAP were screened for transporter expression. Similar changes in

expression of transporters to those seen in mice were also observed in humans, with Mrp4 being the most significantly induced transporter (Figure 2). This served to validate our mouse model of APAP hepatotoxicity as it relates to transport protein expression and regulation.

We have also identified regulatory mechanisms responsible for changes in transport protein expression in response to APAP treatment. Our studies have demonstrated that Nrf2, a transcription factor that induces expression of antioxidant and detoxification enzymes in response to oxidative stress contributes to Mrp4 induction by APAP. We also demonstrated that signaling molecules originating from Kupffer cells, the liver's resident macrophages, mediate Mrp4 induction.
Our data also show a potentially novel role for Mrp4 in the development of tolerance to APAP toxicity. Double immunochemical analysis of liver sections from mice that are tolerant to

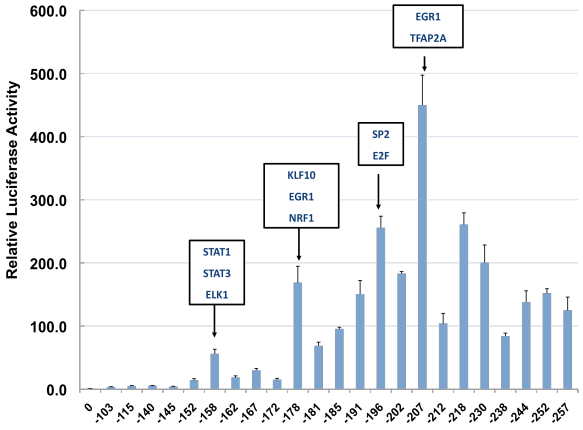

Figure 3. Human MRP4 (hMRP4) reporter plasmids activation. *pGL4-MRP4-Luc reporter plasmids were constructed by PCR cloning and transiently transfected in HepG2 cells. Basal promoter control activation was measured in untreated HepG2 cells. In silico analysis showed that activating transcription factors STAT1, SP2, AP2 and NRF1 and their corresponding cis-elements in human MRP4 gene promoter-proximal region are involved in activation of hMRP4*

toxic APAP re-exposure show that enhanced Mrp4 expression is confined to hepatocytes undergoing compensatory cell replication around the central vein. We observed that when cell proliferation is blocked with the anti-mitotic agent colchicine, not only the susceptibility of pre-conditioned mice to APAP is restored, but also Mrp4 induction is prevented. One of our future goals is to better define the relationship between Mrp4 induction, compensatory cell replication and tolerance to APAP toxicity. We have speculated that Mrp4 induction provides a doorway for the release of signaling molecules from stressed hepatocytes to increase proliferation and repair, as well as increase defense mechanisms in surrounding tissue.

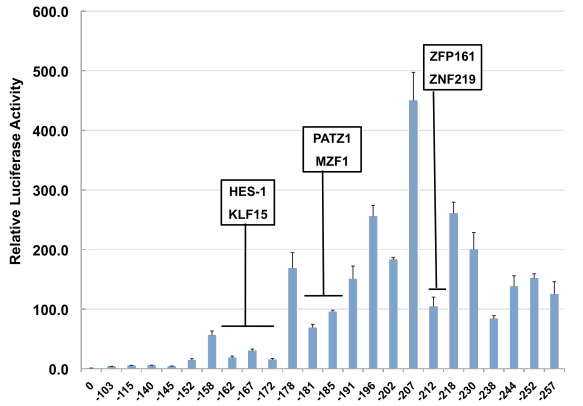

Figure 4. Human MRP4 (hMRP4) reporter plasmids activation. *pGL4-MRP4-Luc reporter plasmids were constructed by PCR cloning and transiently transfected in HepG2 cells. Basal promoter control activation was measured in untreated HepG2 cells. In silico analysis showed that activating transcription factors STAT1, SP2, AP2 and NRF1 and their corresponding cis-elements in human MRP4 gene promoter-proximal region are involved in activation of hMRP4 transcription.*

More recently, we constructed and assayed human MRP4 (hMRP4)-luciferase reporter gene plasmids containing upstream regulatory sequences of different lengths. Basal promoter plasmid control activation was measured in untreated HepG2 cells. Our results show that the promoter proximal region

of hMRP4 is constitutively active, while the distal region is repressive (Figures 3 and 4). We also determined that the promoter region contains many putative transcription factor binding motifs, such STAT1, EGR1, SP2 and several sites for the nuclear respiratory factor-1 (NRF1). Of all transcription factors examined, NRF1 and HES1 had the most profound effect on MRP4 gene expression.

NRF1 is a transcription factor that regulates the expression of nuclear genes encoding mitochondrial proteins involved in bioenergetics. Recent transient transfection studies show that overexpression of NRF1 induces hMRP4 gene expression and regulates hMRP4 gene expression through direct binding to NRF1 sites in the upstream regulatory sequence of hMRP4. As for repressive transcription factors, we have done a preliminary characterization of the effect of HES1 on hMRP4 gene expression. HES-1 is a mammalian homolog of the Drosophila hairy and enhancer of split 1. HES1 is a transcriptional repressor of genes that has been shown to play a role in stem cell differentiation and cell proliferation. Transient transfection and reporter construct activation assays show that HES-1 overexpression significantly repressed the basal activation of all MRP4 reporter constructs examined.

Our most recent and exciting studies directly address the functional consequences of MRP4 induction. Stable transfection of a human immortalized hepatocyte cell line (HC04 cells) with our newly constructed human MRP4 expression plasmid results in enhanced resistance to oxidative stress toxicity induced by tert-butyl hydroperoxide. This is the first indication that overexpression of MRP4 confers tolerance to oxidative stress. One of our future goals is to identify molecules undergoing efflux via MRP4 in cells with enhanced protein expression. Such molecules could provide the paracrine signaling we hypothesized is crucial to hepatoprotection and compensatory hepatocellular proliferation.

Since Mrp4 is the most significantly induced transporter by APAP and its overexpression confers resistance to oxidative stress-mediated toxicity, our transporters research is now centered on Mrp4 regulation and function. Our future studies (next 5 years and the subject of our competing renewal on drug transporters) are aimed at further characterizing the promoter region of human MRP4 and to better define the role of the transcription factors NRF1 and HES1 in MRP4 regulation under conditions of oxidative stress. Other key studies planned will investigate the role of Mrp4 in APAP hepatotoxicity using Mrp4 knockout mice and the ability of these mice to develop resistance to APAP toxicity by pre-exposing the mice to mildly hepatotoxic doses of APAP. We also plan to identify specific substances transported out of hepatocytes via MRP4 with potential hepatoprotective and/or cell proliferative functions using in vitro overexpressing cell systems and metabolomic approaches. Our goal for these studies is to identify compounds undergoing efflux in greater amounts by MRP4 transfected cells in response to oxidative stress in comparison to non-transfected control treated cells. Such compounds will then be subjected to in depth mechanistic studies examining their ability to confer cytoprotection to surrounding cells and also their ability to stimulate compensatory cell proliferation.

b. Hepatoprotection by peroxisome proliferators

Clofibrate (CFB) is a hypolipidemic drug that belongs to a class of compounds known as peroxisome proliferators, which are of great toxicological interest because of their ability to produce liver cancer in rodents. Our laboratory has shown that treatment of mice with

CFB affords protection against acetaminophen (APAP) hepatotoxicity. A gene array analysis was performed in mice pretreated with CFB and challenged with a toxic dose of APAP. The result of this array analysis revealed that the expression of a particular gene, vanin-1 (Vnn1), was upregulated several folds in animals exhibiting this CFB-mediated resistance.

Vnn1 is a membrane-bound pantetheinase, responsible for the hydrolysis of pantetheine to pantothenic acid (Vitamin B5) and cysteamine, an antioxidant. Because of this function, Vnn1 can be regarded as a cytoprotective gene against oxidative stress. However, in addition to this cytoprotective role, Vnn1 has also been shown to have proinflammatory effects. Vnn1 is known to assist in the extravasation of inflammatory cells to sites of injury. These functions of Vnn1 and their possible involvement in the peroxisome proliferator-mediated mechanism of protection are summarized in Figure 5.

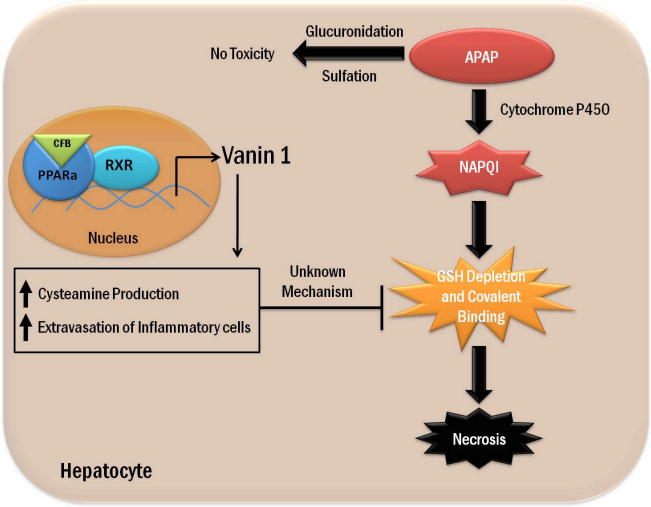

Figure 5: Hypothesis of the mechanism of protection by peroxisome proliferators in acetaminophen hepatotoxicity.

The main goal of recent on-going studies is to examine how the expression and function of Vnn1 affects the susceptibility of the liver to APAP toxicity. The use of complementary in vivo and in vitro techniques is expected to determine if the potential hepatoprotective function of Vnn1 is relevant to humans. In order to investigate the mechanistic role of Vnn1 in APAP hepatotoxicity following CFB treatment, we have initiated studies in collaboration with an investigative team in Marseille, France that developed a knockout mouse model for Vnn1. We determined that these mice have altered susceptibility to APAP toxicity. The absence of Vnn1 results in higher susceptibility to APAP hepatotoxicity and reduced recruitment of inflammatory cells to the site of injury. On-going and future studies will define the role of Vnn1 in hepatoprotection conferred by CFB treatment through a combination of in vivo and in vitro techniques and to understand the relevance of these findings to human liver. We will examine the regulatory effect of Vnn1 on cysteamine and GSH synthesis in both mouse and human liver cells in cells overexpressing or alternatively knocked-down for Vnn1 expression.

These recent results indicate that Vnn1 function is essential for hepatocyte survival during exposure to hepatotoxicants. Although peroxisome proliferator-type responses in liver are known to be species-specific (with rodents showing high susceptibility to these effects), our studies have identified Vnn1 as a gene with potentially important implications to drug-induced liver injury. Collectively, this research can provide foundational knowledge for pursuing Vnn1 as a novel therapeutic target for the treatment of acute liver diseases involving oxidative stress and inflammation.