BIOGRAPHICAL SKETCH

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NAME: LASKIN, JEFFREY D

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

POSITION TITLE: Distinguished Professor of Environmental & Occupational Health & Justice

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
New York University, NY	B.S.	05/1973	Chemistry & Biology
Roswell Park Cancer Institute, SUNY at Buffalo, NY	Ph.D.	09/1977	Pharmacology
Columbia University, NY	postdoctoral	05/1981	Chemical Biology

A. Personal Statement

I have been working in the fields of pharmacology and toxicology for over 40 years. I have been involved in developing biochemical and molecular techniques for assessing mechanisms of toxicity. Many of the mechanisms we study are directed towards understanding chemical-induced inflammation and tissue injury. I have expertise in mechanistic toxicology and biochemical toxicology; this includes DNA as a target for toxicants, areas that I teach in the Joint Graduate Program in Toxicology at Robert Wood Johnson Medical School/Rutgers University School of Pharmacy and Rutgers University School of Public Health. I have been actively working with JGPT graduate students on projects related to chemical threat agents as the field relates to protecting civilian populations against exposures highly toxic chemical agents. Projects with the students have focused on mustard vesicants and organophosphates requiring activation by the cytochrome P450 system. Using sulfur mustard and nitrogen mustard, mechanisms by which these agents modify DNA and proteins in target cells are being investigated. Mustards are bifunctional DNA alkylating agents, biochemical techniques to characterize DNA damage signaling and mechanisms of DNA repair in target tissues which include the skin, lung and eyes are being studied. Techniques in LC-MS/MS to identify mustard-induced chemical modifications in DNA damage signaling proteins, focusing particularly on antioxidants and p53 as these proteins control many genes important in DNA repair are being used. Using techniques in flow cytometry, pathways in the cell cycle particularly sensitive to mustard vesicants in target cells have been identified. This information is being used in attempts to block mustard vesicant toxicity as this may lead to the development of effective therapeutic countermeasures.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

1981-1993 Assistant Professor – Associate Professor – Professor; Environmental & Occupational Medicine, UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ
1982- Member of the Graduate Faculty, Rutgers University, Graduate Programs in Toxicology, Pharmacology, Biochemistry, Microbiology
1986- Member Environmental and Occupational Health Sciences Institute (EOHSI), Rutgers University
1995-2015 Professor & Chief, Division of Toxicology, Environmental & Occupational Medicine, UMDNJ Robert Wood Johnson Medical School, Piscataway, NJ
1995- Member of the Cancer Institute of New Jersey
1997-2013 Member of the Corporation of the Marine Biological Laboratory, Woods Hole, MA

2003-	Deputy Director, Joint Graduate Program in Toxicology, Rutgers University
2005-	Director, Division of Toxicology, Environmental and Occupational Health Sciences Institute
2006-	Center Director, Rutgers University CounterACT Research Center of Excellence
2007-	Founding member, Woods Hole Toxicology Forum, Woods Hole, MA
2007-	Founding member and Executive Committee member, University Center for Disaster Preparedness and Emergency Responses (UCDPER)
2008-2013	Member, Executive Committee; NJ Universities Homeland Security Research Consortium
2014-present	Rutgers Institute for Emergency Preparedness and Homeland Security, Internal Advisory Board
2015-2017	Professor; Environmental & Occupational Health, Rutgers University School of Public Heath, Piscataway, NJ
2015-2018	Chief, Division of Toxicology, Environmental & Occupational Health, Rutgers University School of Public Health, Piscataway, NJ
2017-present	Distinguished Professor, Environmental & Occupational Health & Justice, Rutgers University School of Public Health, Piscataway, NJ

Other Experience/NIH Grant Reviews and Professional Memberships

2007	NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases Roundtable on Wound Healing
2007-2008	Department of Defense, DTRA Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD) Scientific Review: Respiratory and Systemic Therapeutics
2008	NIH Peer Review Committee: Allergy, Immunology & Transplantation Research Review
2008	NIH Peer Review Committee: CounterACT review ZNS1 SRB-R
2009	NIH Peer Review Committee: NIEHS ONES ZES1 JAB-G-R3
2009	NIH Peer Review Committee: NIEHS ONES ZES1 TN G T1 C
2009	NIH Peer Review Committee: ZRG1 IMST-A
2009-2012	NASA Advanced Environmental Health/Advanced Food Technology Committee, Houston, TX,
2009	Conference organizer, “Fourth International Conference on Nitrosative and Oxidative Stress in Disease”, New York, NY (sponsored: New York Academy of Sciences), 10/28/09-10/30/09
2011	NIH Peer Review Committee: CounterACT review, ZRG1 MDCN-B (55)
2011	NASA International Space Station Air Quality and Analytical Instrumentation Review
2012	NIH Study Section, Microphysiological Systems Review, ZRG1 BST-N (50)
2015	NIH Study Section, CounterACT review ZNS1 SRB-R
2015	NIH Study Section (Chair), CounterACT Special Emphasis Panel/Scientific Review Group ZRG1 MDCN-B (55)
2016	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01), ZRG1 MDCN-55
2016	NIH Study Section (Chair), PAR-15-315: CounterACT Exploratory Grants, ZRG1 MDCN-B-55
2017	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U54), ZRG1 MDCN-55
2017	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01), ZRG1 MDCN-55
2017	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (R21), ZRG1 MDCN-55
2018	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (R21), ZRG1 MDCN-55
2019	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (R21), ZRG1 MDCN-55
2020	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01), ZRG1 MDCN-55
2020	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U54), ZRG1 MDCN-55
2022	NIH Study Section, Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects, DKUS-P 50R, Chair
2022	NIH Study Section, SuRe R16 Excellence Awards

C. Contributions to Science

1. Mechanisms mediating chemical redox cycling

Many tissues, particularly the lung and liver, are sensitive to redox-active chemicals, including bipyridyl herbicides such as paraquat, nitroaromatic compounds, and various quinones. In the lung, these chemicals can induce alveolar inflammation, epithelial cell damage, pneumonia, pulmonary hypertension, and fibrosis. Toxicity is thought to result from an accumulation of these chemicals in target cells and subsequent enzyme-mediated redox cycling and the generation of reactive oxygen species. In the redox cycling process, one electron reduction of a redox-active chemical generates radical ions. Under aerobic conditions, these radicals rapidly react with oxygen generating superoxide anion and the parent compound. Spontaneous and enzyme-mediated dismutation of superoxide anion leads to the formation of hydrogen peroxide and in the presence of trace metals, hydrogen peroxide generates highly toxic hydroxyl radicals. Our laboratories have been characterizing mechanisms of redox cycling by NADPH cytochrome P450 reductase and cytochrome P450 enzymes (Mishin et al., 2014). We have identified distinct mechanisms by which this enzyme mediates electron transfer reactions. The complete complement of enzymes in tissues such as the lung and liver that participate in chemical redox cycling has not been clearly established. Additional enzymes that our laboratories have identified as mediating chemical redox cycling are sepiapterin reductase and dicarbonyl/L-xylulose reductase (Yang et al., 2013, 2015; Yang et al., 2017).

- Mishin V, Heck DE, Laskin DL, **Laskin JD**. Human recombinant cytochrome P450 enzymes display distinct hydrogen peroxide generating activities during substrate independent NADPH oxidase reactions Toxicol Sci. 141(2):344-352, 2014. PMC4271041
- Yang S, Jan YH, Gray JP, Mishin V, Heck DE, Laskin DL, **Laskin JD**. Sepiapterin reductase mediates chemical redox cycling in lung epithelial cells. J Biol Chem. 288(26):19221-19237, 2013. PMC3696693
- Yang S, Jan YH, Mishin V, Richardson JR, Hossain MM, Heindel ND, Heck DE, Laskin DL, **Laskin JD**. Sulfa drugs inhibit sepiapterin reduction and chemical redox cycling by sepiapterin reductase. J Pharmacol Exp Ther. 352(3):529-540, 2015. PMC4352594
- Yang S, Jan YH, Mishin V, Heck DE, Laskin DL, **Laskin JD**. Diacetyl/l-xylulose reductase mediates chemical redox cycling in lung epithelial cells. Chem Res Toxicol. 30:1406-1418, 2017. PMC5708134

2. Developing countermeasures to mitigate sulfur mustard toxicity

Sulfur mustard (SM) is a vesicating chemical warfare agent that is relatively easy to synthesize, stockpile, and deliver. Therefore, the development of approaches to counter its acute and chronic toxicities is a high priority. SM was first used as a chemical weapon during World War I, where pulmonary, dermal and ocular toxicity was reported. While ocular and skin lesions in exposed subjects are debilitating, most mortality and morbidity following SM exposure is attributable to damage to the respiratory tract. Early descriptions of acute lung injury included intense inflammation, epithelial necrosis, ulceration of the trachea and sloughing of the tracheal mucous membrane, and bronchioles filled with fibrin and pus. The characteristic response of human skin to SM involves erythema of delayed onset, followed by edema with inflammatory cell infiltration, the appearance of large blisters in the affected area, and a prolonged healing period. SM causes short-term effects in the eye, including pain, tearing, photophobia, blepharospasm, and compromised vision. Our laboratories have been investigating mechanisms by which SM and the related analog, nitrogen mustard, induce toxicity with the aim of developing effective drugs to counter toxicity. In the skin, eye and lung, we have been characterizing cytokines and lipids as mediators of mustard-induced tissue injury (Composto et al., 2016; Wohlman et al. 2016; Wahler et al., 2020). We have discovered that histone modifications are critical for mediating macrophage activation in the lung (Venosa et al., 2017). In the skin, we have found that endocannabinoids are important mediators of toxicity (Wohlman et al., 2016), while the basement membrane is a key target of vesicant toxicity in the eye. We have demonstrated that inhibitors of macrophage activation and lipid mediator production show promise as countermeasures against vesicant-induced tissue injury.

- Wohlman IM, Composto GM, Heck DE, Heindel ND, Lacey CJ, Guillon CD, Casillas RP, Croutch CR, Gerecke DR, Laskin DL, Joseph LB, **Laskin JD**. Mustard vesicants alter expression of the endocannabinoid system in mouse skin. Toxicol Appl Pharmacol. 303:30-44, 2016. PMC4947375
- Venosa A, Gow JG, Hall L, Malaviya R, Gow AJ, **Laskin JD**, Laskin DL. Regulation of nitrogen mustard-induced lung macrophage activation by valproic acid, a histone deacetylase inhibitor. Toxicol Sci. 157(1):222-234, 2017. PMID: 28184907. PMC6075217

- Wahler G, Heck DE, Heindel, ND, Laskin DL, **Laskin, JD**, Joseph LB, Antioxidant/stress response in mouse epidermis following exposure to nitrogen mustard. Exp Mol Pathol 2020, 114:104410. PMID: 32113906 PMC7237310
- Jan YH, Heck DE, An Y, Laskin DL, **Laskin JD**. Nitrogen mustard alkylates and cross-links p53 in human keratinocytes. Chem Res Toxicol. 2022, 35(4):636-650. PMID: 35312310

3. Role of macrophages in ozone mediated lung toxicity

Ozone is a ubiquitous urban air pollutant and a major public health concern, especially in the elderly and in individuals with existing lung disease. Ozone causes oxidation of membrane lipids and proteins resulting in damage to the respiratory epithelium and the alveolar epithelial layer (Sunil et al., 2015). This is associated with an accumulation of inflammatory macrophages in the lung, which have been implicated in the pathogenesis of ozone toxicity (Laskin et al., 2019). Macrophage trafficking to sites of tissue injury depends on chemokines released at these sites and chemokine receptors present on responding cells. Our laboratories have been characterizing macrophage populations accumulating in the lung following ozone-induced injury and cytokines/chemokines and their receptors in mediating macrophage trafficking. For example, one of the most potent chemokines identified for monocytes and macrophages is macrophage chemotactic protein (MCP)-1 or CCL2, which acts by binding to the chemokine receptor, CCR2, present on responding cells. We identified CCL2 as a key mediator of ozone-induced macrophage accumulation in rodent lung, we also found that inflammatory macrophage accumulation in the lung is blunted in mice lacking CCR2, and that this is correlated with reduced injury and oxidative stress providing novel insights into inflammatory mechanisms contributing to tissue injury induced by ozone (Francis et al. 2017). Other mediators that we have identified in the lung important in mediating ozone toxicity including TNF-α and interleukin-1 as well as the signaling molecules in extracellular vesicles known to mediate toxicity (Andres et al., 2020).

- Francis M, Groves AM, Sun R, Cervelli JA, Choi H**, Laskin JD**, Laskin DL. CCR2 regulates inflammatory cell accumulation in the lung and tissue injury following ozone exposure. Toxicol Sci. 155(2):474-484, 2017. PMC5291213
- Laskin DL, Malaviya R, **Laskin JD**. Role of macrophages in acute lung injury and chronic fibrosis induced by pulmonary toxicants. Toxicol Sci. 2019, 168:287-301. PMC6432864
- Andres J, Smith LC, Murray A, Jin Y, Businaro R, **Laskin JD**, Laskin DL. Role of extracellular vesicles in cell-cell communication and inflammation following exposure to pulmonary toxicants. Cytokine Growth Factor Rev. 2020 51:12-18, 2020. PMC7052797
- Carnino JM, Lee H, Smith LC, Sunil VR, Rancourt RC, Vayas K, Cervelli J, Kwok ZH, Ni K, **Laskin JD**, Jin Y, Laskin DL. Microvesicle-derived miRNAs regulate proinflammatory macrophage activation in the lung following ozone exposure. Toxicol Sci. 2022, 187(1):162-174. PMID: 35201360

4. Identifying targets of acetaminophen metabolites in the liver

Acetaminophen (APAP) is a widely used analgesic and antipyretic agent considered safe at therapeutic doses; however, overdose can cause severe hepatotoxicity leading to acute liver failure (Laskin et al., 2011, Dragomir et al., 2012, Mandal et al., 2016). At therapeutic doses, APAP is largely eliminated via sulfation and glucuronidation reactions in the liver. APAP also undergoes cytochrome P450-mediated biotransformation to N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive electrophile. APAP overdose saturates the conjugation pathways resulting in increased levels of NAPQI, which readily depletes hepatic glutathione (GSH). This results in covalent modification of nucleophilic sites on hepatic cellular proteins by NAPQI and cytotoxicity. Using techniques in LC-MS/MS, our laboratories have been identifying proteins modified by NAPQI to understand mechanisms of APAP toxicity. We have identified the thioredoxin system as an important NAPQI target (Jan et al., 2014). Composed of NADPH, thioredoxin reductase (TrxR), and thioredoxin (Trx), it functions, at least in part, to protect cells against oxidative stress. TrxR contains selenocysteine (Sec) in its C-terminal redox center, a highly accessible target for electrophilic modification. We found that APAP treatment of mice was associated with a marked inhibition of hepatic TrxR. Using purified rat liver enzyme, TrxR inactivation was correlated with the metabolic activation of APAP by cytochrome P450 indicating that enzyme inhibition was due to APAP-reactive metabolites. LC-MS/MS analysis demonstrated that NAPQI modified cysteine 59, cysteine 497, and selenocysteine 498 residues in the redox centers of TrxR, resulting in enzyme inhibition (Jan et al., 2014). Further studies in our laboratories are aimed at determining if thiol protective agents such as N-acetylcysteine and glutathione protect TrxR and as a result, mitigate APAP intoxication.

- Laskin DL, Sunil VR, Gardner CR, **Laskin JD**. Macrophages and tissue injury: agents of defense or destruction? Annu Rev Pharmacol Toxicol. 51:267-288, 2011. PMC3670679
- Dragomir AC, Sun R, Choi H, **Laskin JD**, Laskin DL. Role of galectin-3 in classical and alternative macrophage activation in the liver following acetaminophen intoxication. J Immunol. 189(12):5934-5941, 2012. PMC3518653
- Jan YH, Heck DE, Dragomir AC, Gardner CR, Laskin DL, **Laskin JD**. Acetaminophen reactive intermediates target hepatic thioredoxin reductase. Chem Res Toxicol. 27(5):882-894, 2014. PMC4033643
- Mandal M, Gardner CR, Sun R, Choi H, Lad S, Mishin V, **Laskin JD**, Laskin DL. The spleen as an extramedullary source of inflammatory cells responding to acetaminophen-induced liver injury. Toxicol Appl Pharmacol. 304:110-120, 2016. PMC5147741

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