BIOGRAPHICAL SKETCH

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NAME: Debra L. Laskin

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

POSITION TITLE: Distinguished Professor and Chair

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.A.	05/1975	Psychology
City University of New York, NY	M.A.	09/1977	Biopsychology
Medical College of Virginia, VCU, Richmond, VA	Ph.D.	05/1980	Pharmacol/Toxicology
Wistar Inst., Univ. Pennsylvania, Philadelphia, PA	Postdoc	06/1982	Immunology

A. Personal Statement

My research is focused on elucidating inflammatory mechanisms underlying acute injury and the pathogenesis of disease induced by toxicants, specifically in the lung and liver. For my work, various pulmonary and hepatic toxicants are utilized, including mustards, ozone, particulates, and chlorine in the lung and endotoxin and acetaminophen in the liver. I am specifically interested in the role of macrophages and inflammatory mediators in the pathogenic response to toxicants. For our studies, we use rodent and in some models human models of exposure and techniques in flow cytometry/cell sorting, molecular biology, and biochemistry to characterize the phenotype and functioning of inflammatory macrophages, and mechanisms regulating their activity. Studies with transgenic mice lacking key inflammatory proteins and chimeric mice generated by bone marrow transplantation are also being used to identify specific inflammatory mediators and macrophage subset contributing to tissue injury and repair. The overall goal of my research is to harness the pathologic activity of macrophages and redirect it towards promoting inflammation resolution and tissue repair.

I have been working in the fields of pharmacology and toxicology for 40 years. I have a broad background and training in these disciplines, with specific expertise in immunology, pulmonary and hepatic pathophysiology and disease pathogenesis. My doctoral work at the Medical College of Virginia was focused on immunotoxicology. As a postdoctoral fellow at the University of Pennsylvania's Wistar Institute, I was trained in immunology and flow cytometry/cell sorting. Since arriving at Rutgers University in 1982, I have been continuously funded by NIH through multiple R01 grants. I have made several seminal contributions to our understanding of the role of macrophages and inflammation in chemically-induced tissue injury and have received many awards for my work including the Society of Toxicology (SOT) Achievement Award, the SOT Frank Blood (Board of Publications Award), the Burroughs Welcome Toxicology Scholar Award, the SOT Inhalation and Respiratory Specialty Section Career Achievement Award, the SOT Mechanisms Career Achievement Award, the ASPET Toxicology Division Career Award and most recently the Rutgers Biomedical Health Science Lifetime Distinguished Achievement Award. I have also written numerous influential invited reviews on macrophages and tissue injury, which are widely referenced.

I am actively involved in research training and mentoring and was honored in 2014 by the SOT with the Women in Toxicology Mentoring Award, in 2017 with SOT Education Award, and in 2021 with Rutgers Biomedical Health Sciences Distinguished Mentoring Award. I have trained 13 postdoctoral fellows, 24 doctoral students and numerous undergraduates. My trainees have won awards for their work at various National meetings, including SOT, ASPET, and the Society for Leukocyte Biology. I am an active member of the Joint Graduate Program in Toxicology at Rutgers, and a co-investigator on our NIEHS funded T32 Toxicology Training Grant, as well as Co-PI on an R25 grant from NIEHS to support our summer undergraduate research program. In addition to serving as Deputy Director of the Rutgers NIEHS P30 Center during the past three funding cycles (2006-2023), I am Co-director of the Career Development Program and

have mentored numerous junior basic science and clinical faculty who have successfully competed for NIH funding. I was appointed to the NJ ACTS Academy of Mentors, where I am a member of the Pilot Project Management Committee.

- **Laskin, D.L.** 2009. Macrophages and inflammatory mediators in chemical toxicity: a battle of forces. Chem Res Toxicol 22:1376-1385. PMCID: PMC2787782
- **Laskin, D.L.**, Malaviya, R., Laskin, J.D. 2015. Pulmonary macrophages. In Comparative Biology of the Normal Lung, 2nd edition, edited by R. Parent. UK: Elsevier. 629-649.
- **Laskin, D.L.,** Malaviya, R., Laskin, J.D. 2019. Role of macrophages in acute lung injury and chronic fibrosis Induced by pulmonary toxicants. Toxicol Sci 168:287-301. PMCID: PMC6432864; ***(*highlighted by journal as "Impactful Research in Toxicology" based in citations; September, 2021)***
- Malaviya, R., Kipen, H.M., Businaro, R., Laskin, J.D., **Laskin, D.L**. 2020. Pulmonary toxicants and fibrosis: innate and adaptive immune mechanisms. Toxicol Appl Pharmacol 498:115272. PMCID: PMC9960630.

Ongoing Research Support

NIH R01ES033698; D.L. Laskin (PI); 2/15/22-11/30/26; Harnessing Inflammatory Macrophages to Thwart Lung Disease caused by Chronic Ozone Exposure. *Involves studies on the role of macrophages in chronic ozone induced asthma and emphysema.*

NIH R01ES004738; D. L. Laskin (PI); 9/1/22-8/30/27; Activated Macrophages and Ozone Toxicity; *Involves studies on the role of macrophages and inflammatory mediators in lung injury induced by acute ozone exposure in rodents and humans.*

NIH U54AR055073; J.D. Laskin (PI); 9/1/21-8/31/25; Rutgers CounterACT Research Center of Excellence; Supports the development of therapeutics to treat mustard poisoning. Dr. D. Laskin's project focuses on identifying novel targets of mustard injury in the lung. Role: Co-I.

CDC U01OH012072; J. Sunderram (PI); 7/1/21- 6/30/24; Obstructive Sleep Apnea and WTC dust: Does Chronic Intermittent Hypoxia exacerbate WTC dust induced lung injury? *Analyzes the effects of intermittent hypoxia on WTC dust exposure induced lung injury in a mouse model.* Role: Co-I

B. Positions, Scientific Achievements, and Honors

Positions and Employment

2006–pres	Deputy Director, Rutgers NIEHS P30 Center for Environmental Exposures and Disease
2003–pres	Chair, Dept. Pharmacol & Toxicol, School of Pharmacy, Rutgers University
2000–pres	Distinguished Professor, Pharmacol & Toxicol, School of Pharmacy, Rutgers University
1986–	Member, Rutgers Environmental and Occupational Health Sciences Institute (EOHSI)
1985–pres	Founding Director, Rutgers Flow Cytometry/Cell Sorting & Confocal Microscopy Core
1982–pres	Faculty Member, Rutgers Graduate School, Toxicology, Molecular Biosciences, Nutrition
1982–2000	Assist/Assoc/Full Professor, Pharmacol & Toxicol, School of Pharmacy, Rutgers University

Other Activities including Participation in Federal Committees (**Selected Recent**)

2018-2020	VP/President/Past President, Inhalation Respiratory Specialty Section, Society of Toxicology
June 2019	Organizer, 13th Annual CounterACT Network Research Symposium, June 15-17, NYAS, NY
2016-2017	Vice President, Inhalation and respiratory Specialty Section, Society of Toxicology
July 2015	NIEHS Pathway to Independence Award (K99/R00) review panel
June 2015	Conference organizer, 9th Annual CounterACT Network Research Symposium, June 15-17, New York Academy Sciences, NY
2014-2019	Member, NIH Systemic Injury by Environmental Exposures (SIEE) Study Section
2014-2015	Member, Program Committee, ASPET
2013–2015	Chair-Elect/Chair, Toxicology Division, ASPET
Feb/Jun 2013	NIH Systemic Injury by Environmental Exposures (SIEE) Special Emphasis Panel
Jan 2012	NIH Environmental Health and Toxicology Working Group
Oct 2011	NIH Lung Injury and Repair Review Panel
2009–2012	Continuing Education Committee, Society of Toxicology
Oct. 2009	Conference organizer, "4th International Conference on Nitrosative and Oxidative Stress in Disease", New York Academy of Sciences, 10/28/09-10/30/09

July 2009	NIH Challenge Grant Distinguished Editorial Panel
July 2008	NIH Drug Induced Liver Disease Review Committee,
2007–2012	Editorial board member, Annual Review Pharmacology and Toxicology
Oct 2007	NIH Blue Ribbon Panel, NIAID Office of Biodefense Research Medical Countermeasures Against Toxic Vesicants Workshop
May 2005	NIH NIEHS Special Emphasis Panel
2001– 2003	Awards Committee, Society of Toxicology
2000–2003	External Advisory Committee, Univ. Maryland, USEPA Particulate Center
1999	Pulmonary Toxicity Workshop, Lovelace Respiratory Res. Inst., NM
Sept 1999	External Review Comm., Oxidant Injury Program, HELD, NIOSH, Morgantown, WV
1998–2003	Science Advisory Board, Clean Air Scientific Advisory Committee, EPA
1996–2009	Chair, Research Committee, New Jersey Thoracic Society
1994–1996	Councilor (elected), Society of Toxicology
1993–1995	Secretary (elected), Society for Leukocyte Biology
1993–1997	Section Editor, Journal of Leukocyte Biology
1992–1994	Secretary/Treasurer, Mechanisms Specialty Section, Society of Toxicology
1992–pres	Editorial Board, Journal Toxicology and Environmental Health
1990–1993	Councilor (elected), Society for Leukocyte Biology
1989–pres	Editorial Board/Associate Editor, Toxicology and Applied Pharmacology

Honors and Awards

2022	Rutgers Biomedical Health Sciences Lifetime Distinguished Achievement Award
2021	Rutgers Biomedical Health Sciences Distinguished Mentor Award
2021	ASPET, Toxicology Division, Career Achievement Award
2021	Society of Toxicology Immunotoxicology Specialty Section Paper of the Year Award, Regulation of Lung Macrophage Activation and Oxidative Stress following Ozone Exposure by Farnesoid X Receptor, *Toxicological Sciences, 177: 441-453, 2020*.
2019	Society of Toxicology Inhalation and Respiratory and Mechanisms Specialty Sections Paper of the Year Award; “Functional Evidence of Pulmonary Extracellular Vesicles in Infectious and Noninfectious Lung Inflammation”, *Journal of Immunology, 20: 1500-1509, 2018*.
2018	Society of Toxicology Mechanisms Specialty Section Career Investigator Award
2017	New Jersey Health Foundation Excellence in Research Award
2017	Society of Toxicology Education Award
2015	Society of Toxicology Inhalation and Respiratory Specialty Section Career Investigator Award
2014	Society of Toxicology Women in Toxicology Mentoring Award
2009	Rutgers University Board of Trustees Excellence in Research Award
2007	Named Roy A. Bowers Endowed Chair, Ernest Mario School of Pharmacy, Rutgers University
1999	Dolph Adams Award, Society for Leukocyte Biology (for the most cited research publication in the society’s journal; Journal Leukocyte Biology)
1993-1998	Burroughs Wellcome Toxicology Scholar Award
1991	Society of Toxicology Achievement Award
1989	Society for Leukocyte Biology Young Investigator Research Award
1988	Frank R. Blood Award of the Society of Toxicology (for the best research publication in the society’s journals); renamed Board of Publications Award

C. Contributions to Science

1. Macrophages and chemically-induced hepatotoxicity

An early focus of my research was elucidating the role of macrophages in acute liver injury induced by chemicals and drugs such as acetaminophen (APAP). We were the first to suggest that toxicity is due, not only to direct effects of APAP metabolites on the liver, but also to the actions inflammatory macrophages responding to APAP-induced injury. The implications of this work, published in 1986, were immediately recognized by the Society of Toxicology (SOT) who awarded us the Best Publication of the Year Award in 1988, and awarded me the SOT Achievement Award in 1991, and in 1993, the Burroughs Wellcome Toxicology Scholar Award. My pioneering research played a major role in steering many investigators into considering phagocytes as active participants in the progression of chemically induced tissue injury, and it spawned a series of papers confirming our observations not only in the liver, but in other tissues. Continuing these investigations, several years later we were also the first to report that subpopulations of macrophages accumulating in the liver

following APAP intoxication are important in wound repair and that in their absence, hepatotoxicity is exacerbated. This work generated considerable excitement, as it was the prelude to the current understanding that the activity of macrophage depends on their phenotype (i.e., M1 vs. M2). As more researchers began investigating macrophages and APAP hepatotoxicity, the field became controversial raising the question, do macrophages contribute to or protect against hepatotoxicity? In my review, highlighted on the cover of Chemical Research in Toxicology, this controversy was addressed, providing clear evidence that the contribution of macrophages to APAP hepatotoxicity depends on when the cells appear in the liver and the mediators they encounter, which dictate their phenotype and function. In further studies published in the prestigious Journal of Immunology we precisely characterized different populations of macrophages in the liver after APAP provided definitive evidence supporting this notion.

- Dragomir, A.C., Sun, R., Choi, H., Laskin, J.D., **Laskin, D.L.** 2012. Role of galectin-3 in classical and alternative macrophage activation in the liver following acetaminophen intoxication. J Immunol 189:5934-5941. PMCID: PMC3518653.
- Dragomir, A.C., Sun, R., Mishin, V., Hall, L.B., Laskin, J.D., **Laskin, D.L.** 2012. Role of galectin-3 in acetaminophen-induced hepatotoxicity and inflammatory mediator production. Toxicol Sci 127:609-619. PMCID: PMC3355315.
- Gardner, C.R., Hankey, P., Mishin, V., Francis, M., Yu, S., Laskin, J.D., **Laskin, D.L.** 2012. Regulation of alternative macrophage activation in the liver following acetaminophen intoxication by stem cell-derived tyrosine kinase. Toxicol Appl Pharmacol 262:139-148. PMCID: PMC3377817.
- Mandal, M., Gardner, C.R., Sun, R., Choi, H., Lad, S., Mishin, V., Laskin, J.D., **Laskin, D.L**. 2016. The spleen as an extramedullary source of inflammatory cells responding to acetaminophen-induced liver injury. Toxicol Appl Pharmacol 304:110-120. PMCID: PMC5147741.

2. Macrophages and inflammatory mediators in lung injury induced by environmental pollutants

Our innovative work in the liver prompted us to investigate the role of macrophages and inflammatory mediators in lung toxicity induced by environmental pollutants; although our focus has mainly been on ozone, my group has also studied particulate air pollution. In early pioneering studies, we demonstrated that macrophages play a critical role in ozone toxicity; subsequently, we assessed inflammatory mediators important in the pathogenic response including reactive nitrogen species and tumor necrosis factor alpha. We also demonstrated important roles of transcription factors, NFκB and farnesoid X receptor, in macrophage activation and ozone-induced tissue injury. Remarkably, results from these studies were quite similar to our findings in the liver with APAP. Thus, following acute ozone exposure, we noted the sequential accumulation of proinflammatory and proresolution macrophages in the lung. Moreover, while inhibiting proinflammatory macrophages protected against ozone toxicity, blocking proresolution macrophages exacerbated tissue injury. These findings indicate that the contribution of macrophages to the pathophysiology of tissue injury is dependent on macrophage phenotype and the timing of their appearance in the lung. These data also support the notion that similar inflammatory mechanisms contribute to the response to toxicants in different target tissues.

- Francis, M., Sun, R., Cervelli, J.A., Choi, H., Mandal, M., Abramova, E.V., Gow, A.J., Laskin, J.D., **Laskin, D.L.** 2017. Role of spleen-derived macrophages in ozone-induced lung inflammation and injury. Toxicol Sci 155:182-195. PMCID: PMC6080856 (***editor's highlight***)
- Francis, M., Groves, A.M., Sun, R., Cervelli, J.A., Choi, H., Laskin, J.D., **Laskin, D.L.** 2017. CCR2 regulates inflammatory cell accumulation in the lung and tissue injury following ozone exposure. Toxicol Sci 155:474-484. PMCID: PMC5291213 (***editor's highlight***)
- Francis, M., Guo, G., Kong, B., Abramova, EV, Cervelli, J.A., Gow, A.J., Laskin, J.D., **Laskin, D.L.** 2020. Regulation of lung macrophage activation and oxidative stress following ozone exposure by farnesoid X receptor. Toxicol Sci 177:441-453. PMCID: PMC32984886 (***Paper of the Year, SOT Immunotox SS***)
- Taylor, S., Murray, A., Francis, M., Abramova, E., Guo, C., **Laskin, D.L.**, Gow, A.J. 2022. Regulation of macrophage activation by S-nitrosothiols following ozone-induced injury. Toxicol Appl Pharmacol 457:116281. PMID: 36244437.

3. Role of macrophages and inflammatory mediators in vesicant-induced lung injury and fibrosis

Over the past 16 years, we have made major progress in understanding mechanisms underlying the toxicity of vesicants including nitrogen mustard (NM) and sulfur mustard (SM) in the lung. Our novel findings have significantly advanced the field and have led to the identification of key targets in the lung for the development of countermeasures against these chemical threat agents. As a result of our studies, many investigators in the NIH CounterACT program have begun to look at inflammatory mechanisms of pulmonary injury induced by diverse chemical threats. Our early studies focused on developing an animal model of lung toxicity that

recapitulated the response of humans to inhaled SM. We achieved success initially using NM, and more recently with SM itself. Particularly notable in our studies was that acute lung injury and fibrosis induced by mustards is associated with the sequential appearance of proinflammatory M1 and proresolution/wound repair M2 macrophages in the tissue, suggesting that these cells are involved in the pathologic response to mustard vesicants. Our mechanistic research on also led to the identification of two key proinflammatory proteins involved in the pathogenic response: TNFα and inducible nitric oxide synthase (iNOS). Using pharmacologic inhibitors and transgenic animals, we demonstrated that lung injury and fibrosis could be prevented by targeting these proteins. This work is highly significant as it provides the basis for drug development aimed at targeting these proteins and mitigate vesicant-induced lung injury.

- Malaviya, R., Abramova, E.V., Rancourt, R.C., Sunil, V.R., Napierala, M., Weinstock, D., Croutch, C.R., Roseman, J., Tuttle, R., Peters, E., Casillas, R.P., Laskin, J.D. **Laskin, D.L.** 2020. Progressive lung injury, inflammation and fibrosis in rats following inhalation of sulfur mustard. Toxicol Sci 178:358-374. PMCID: PMC7751178.
- Venosa, A., Smith, L.C., Gow, A.J., Zarbl, H., Laskin, J.D., Laskin, D.L. 2021. Macrophage activation in the lung during the progression of nitrogen mustard induced injury is associated with histone modifications and altered miRNA expression.Toxicol Appl Pharmacol 423:115569. PMCID:PMC8496734.
- Malaviya, R., Bellomo, A., Abramova, E., Croutch, C.R., Roseman, J., Tuttle, R., Peters, E., Casillas, R.P., Sunil, V.R., Laskin, J.D., **Laskin, D.L.** 2021. Pulmonary injury and oxidative stress in rats induced by inhaled sulfur mustard is ameliorated by anti-tumor necrosis factor-α antibody**.** Toxicol Appl Pharmacol 428: 115677. PMCID: PMC8452183.
- Sunil, V.R., Vayas, K.N., Radbel, J., Abramova, E., Gow, A., Laskin, J.D., **Laskin, D.L**. 2022. Impaired energy metabolism and altered functional activity of alveolar type II epithelial cells following exposure of rats to nitrogen mustard. Toxicol Appl Pharmacol 456:116257. PMID: 36174670.

4. Biochemical and molecular mechanisms regulating macrophage activation during the pathogenesis of lung injury and chronic disease induced by pulmonary toxicants

My studies have also contributed to understanding biochemical and molecular mechanisms controlling macrophage activation. Specifically, we identified the transcription factors NFκB, FXR and NR4A1 as key regulators of macrophage activation in the lung following ozone exposure. We have also been investigating epigenetic regulation of macrophages after toxicant exposure including histone modifications and changes in expression of noncoding RNAs, considered the gatekeepers of inflammatory responses. Importantly, we identified several key miRNAs involved in regulating phenotypic activation of macrophages in the lung after exposure to oxidants. These studies point to new molecular targets within macrophages that may be used for therapeutic manipulation of their activity. We have also been investigating cell-cell communication in inflammatory macrophage activation, specifically the role of extracellular vesicles in the transport of regulatory signaling molecules. This timely work is highly relevant since exosomes, a class of microvesicles, are emerging as powerful tools for crossing biological barriers in drug delivery.

- Lee, H., Zhang, D., **Laskin, D.L**., Jin Y. 2018. Functional evidence of pulmonary extracellular vesicles in infectious and noninfectious lung inflammation. J Immunol 201:1500-1509. PMCID: PMC6109965 ***(**Paper of the Year Award; SOT Mechanisms and Inhalation and Respiratory Specialty Sections)***
- Andres, J., Smith, L.C., Murray, A., Jin, Y., Businaro, R., Laskin, J.D., **Laskin, D.L.** 2020. Role of extracellular vesicles in cell-cell communication and inflammation following exposure to pulmonary toxicants. Cytokine Growth Factor Rev 51:12-18. PMCID: PMC7052797.
- Venosa, A., Smith, L.C., Gow, A.J., Zarbl, H., Laskin, J.D., **Laskin, D.L.** 2021. Macrophage activation in the lung during the progression of nitrogen mustard induced injury is associated with histone modifications and altered miRNA expression. Toxicol Appl Pharmacol 423:115569. PMCID: PMC8496734.
- Carnino, J.M., Lee, H., Smith, L.C., Sunil, V.R., Rancourt, R., Vayas, K., Cervelli, J., Kwok, Z.H., Ni, K., Laskin, J.D., Jin, Y., **Laskin, D.L.** 2022. Microvesicle-derived miRNAs regulate proinflammatory macrophage activation in the lung following ozone exposure. Toxicol Sci. 187:162-174. PMCID: PMC9041552.

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