

APPENDIX 1

Related Pulmonary Research Projects funded by ORD:

Julie Bastarache (Nashville, TN) 10/1/2017-9/30/2021
Potential Protective Mechanisms of Tissue Factor in Acute Lung Injury

CHRISTINE M BASMAJIAN (Ann Arbor, MI) 10/01/2016-9/30/2020
Cross-talk between lung natural killer cells and dendritic cells in COPD

Timothy Blackwell (Nashville, TN) 4/1/2014-3/31/2018
Mechanisms driving airway inflammation in chronic lung disease

Michael Borchers (Cincinnati, OH) 10/1/2014-9/30/2018
Natural Killer Cell Functions in COPD

Susmita Chowdhuri (Detroit, MI) 04/01/2015-3/31/2019
Pathophysiology-Guided Therapy for Sleep Apnea in the Elderly

Jeffrey Curtis (Ann Arbor, MI) 4/01/2015-3/31/2019
Modulation of Steroid Suppression by Alveolar Macrophage Efferocytosis

Hubert Forster (Milwaukee, WI) 1/1/2016-12/31/2019
Mechanisms of ventilatory adaptations to chronic hypercapnia

Amit Gaggar (Birmingham, AL) 10/1/2014-9/30/2018
Prolyl Endopeptidase-Mediated Matrix Remodeling and Inflammation in COPD

John Greenland (San Francisco, CA) 4/1/2015-3/31/2020
Immune Mechanisms of Large-airway Lymphocytic Bronchitis

Michael C. Hart (DECATUR, GA) 10/01/2012-9/30/2016
Mechanisms and Consequences of Reduced PPAR gamma in Pulmonary Hypertension

Jeffrey Hasday (Baltimore, MD) 7/1/2013-6/30/2018
Hyperthermia-augmented epithelial apoptosis and acute lung injury

Timothy Hogan (Bedford, MA) 10/1/2016-9/30/2020
A Technology-Assisted Care Transition Intervention for Veterans with Chronic Heart Failure or Chronic Obstructive Pulmonary Disease

John Hoidal (Salt Lake City, UT) 4/1/2013-3/31/2017
The RAGE of COPD

Elizabeth Jacobs (Milwaukee, WI) 4/1/2013-3/31/2017
Novel Diagnostics to Detect Lung Injury

Farrah Kheradmand (Houston, TX) 7/1/2014-6/30/2018
Regulation of Innate and Acquired Immunity in Human COPD and Emphysema

Tim Lahm (Indianapolis, IN) 10/01/2013-9/30/2017
Hypoxia-mediated protective estrogen receptor signaling in pulmonary hypertension

William Lawson (Nashville, TN) 1/1/2013-12/31/2016
Regulation of pulmonary fibrosis by the sonic hedgehog pathway

Patty Lee (West Haven, CT) 1/1/2017-12/31/2020
MIF-mediated Mechanisms in Emphysema

Irina Luzina (Baltimore, MD) 4/1/2014-3/31/2018
Distinct regulation of pulmonary inflammation by isoforms of Interleukin-33

Jason Mateika (Detroit, MI) 1/1/2014-12/31/2017
Circadian Modulation of Breathing Stability and Respiratory Plasticity

Susan Mathai (Denver, CO) 10/1/2017-9/30/2022
Genomic Profiling of Early Pulmonary Fibrosis

Jordan Metcalf (Oklahoma City, OK) 10/1/2014-9/30/2018
Antiviral Immunosuppression by Cigarette Smoke

Toru Nyunoya (Pittsburgh, PA) 1/1/2015-4/30/2018
Role of DNA Repair in COPD

Ray Peebles (Nashville, TN) 7/1/2014-6/30/2018
PGI2 inhibition of pulmonary innate allergic immune responses

Alexa Pragman (Minneapolis, MN) 11/15/2015-11/14/2020
Evaluation of the Oral and Lung Microbiota and Inflammation in Chronic Obstructive Pulmonary Disease Frequent Exacerbators

Robert Paine (Salt Lake City, UT) 04/01/2013-03/31/2017
Molecular regulation of GM-CSF expression in alveolar epithelial cells

Sekhar Pothireddy (Chicago, IL) 7/1/2017-6/30/2021
Role of NRF2 in Alveolar Epithelial Regeneration during Lung Repair

Raju Reddy (Pittsburgh, PA) 7/1/2013-9/30/2018
Role of PPAR-gamma in Smoking-induced COPD Progression and Steroid Resistance

Elizabeth Redente (Denver, CO) 4/1/2015-3/31/2020
Mechanisms of TNF-alpha Mediated Resolution of Pulmonary Fibrosis

David Riches (Denver, CO) 1/1/2017-12/31/2020
Therapeutic Targeting of PTPN13 in Idiopathic Pulmonary Fibrosis

Jesse Roman (Louisville, KY) 04/01/2014-03/31/2018
Nicotine and nicotinic receptors in lung transitional remodeling

Sharon Rounds (Providence, RI) 10/01/2014-9/30/2018
Mechanisms of Cigarette Smoke-Induced Acute Lung Injury

Ruxana Sadikot (Decatur, GA) 7/1/2013-6/30/2017
TREM-1 in Lung Immune Response

David Schwartz (Denver, CO) 10/1/2012-12/31/2016
Genetic and Epigenetic Changes in MUC5B and Fibrosing Interstitial Lung Disease

Yunchao Su (Augusta, GA) 10/1/2014-9/30/2018
Airway and Lung Vascular Remodeling in COPD

Mihaela Teodorescu (Madison, WI) 4/1/2016-3/31/2020
Mechanisms of Chronic Intermittent Hypoxia Induced Airflow Obstruction during Allergic Lower Airway Inflammation

Todd Wyatt (Omaha, NE) 4/1/2017-3/31/2021
Malondialdehyde-acetaldehyde adducts and lung injury

APPENDIX 2

Airborne Hazards and Open Burn Pit Publications From Post Deployment Health Services and Airborne Hazards Center of Excellence (ACHE) War Related Illness and Injury Study Center, New Jersey (NJ-WRIISC)

1. Barth SK, Dursa EK, Bossarte R, Schneiderman A. Lifetime Prevalence of Respiratory Diseases and Exposures Among Veterans of Operation Enduring Freedom and Operation Iraqi Freedom Veterans: Results From the National Health Study for a New Generation of U.S. Veterans. *J Occup Environ Med*. 2016 Dec;58(12):1175-1180.
2. Pugh MJ, Jaramillo CA, Leung KW, Faverio P, Fleming N, Mortensen E, Amuan ME, Wang CP, Eapen B, Restrepo M, Morris MJ. Increasing Prevalence of Chronic Lung Disease in Veterans of the Wars in Iraq and Afghanistan. *Mil Med*. 2016 May;181(5):476-81.
3. Jani N, Falvo MJ, Sotolongo A, Osinubi OY, Tseng CL, Rowneki M, Montopoli M, Morley SW, Mitchell V, Helmer DA. Blast Injury and Cardiopulmonary Symptoms in U.S. Veterans: Analysis of a National Registry. *Ann Intern Med*. 2017 Nov 21;167(10):753-755. doi: 10.7326/M17-0711. Epub 2017 Sep
4. Falvo M, Helmer D, Klein J, Osinubi OY, Ndirangu D, Patrick-DeLuca LA, Sotolongo AM. Isolated diffusing capacity reduction is a common clinical presentation in deployed Iraq and Afghanistan veterans with deployment-related environmental exposures. *Clin Respir J*. 2018 Feb;12(2):795-798. Epub 2016 Sep 27.
5. Liu J, Lezama N, Gasper J, Kawata J, Morley S, Helmer D, Ciminera P. Burn Pit Emissions Exposure and Respiratory and Cardiovascular Conditions Among Airborne Hazards and Open Burn Pit Registry Participants. *J Occup Environ Med*. 2016 Jul;58(7):e249-55.
6. Falvo MJ, Abraham JH, Osinubi OY, Klein JC, Sotolongo AM, Ndirangu D, Patrick-DeLuca LA, Helmer DA. Bronchodilator Responsiveness and Airflow Limitation Are Associated With Deployment Length in Iraq and Afghanistan Veterans. *J Occup Environ Med*. 2016 Apr;58(4):325-8.
7. Falvo MJ, Osinubi OY, Sotolongo AM, Helmer DA. Airborne hazards exposure and respiratory health of Iraq and Afghanistan veterans. *Epidemiol Rev*. 2015;37:116-30. Epub 2015 Jan 14.
8. Santos SL, Helmer D, Teichman R. Risk communication in deployment-related exposure concerns. *J Occup Environ Med*. 2012 Jun;54(6):752-9. Erratum in: *J Occup Environ Med*. 2012 Aug;54(8):1039.
9. Helmer DA, Rossignol M, Blatt M, Agarwal R, Teichman R, Lange G. Health and exposure concerns of veterans deployed to Iraq and Afghanistan. *J Occup Environ Med*. 2007 May;49(5):475-80.

10. Lincoln AE, Helmer DA, Schneiderman AI, Li M, Copeland HL, Prisco MK, Wallin MT, Kang HK, Natelson BH. The war-related illness and injury study centers: a resource for deployment-related health concerns. *Mil Med.* 2006 Jul;171(7):577-85.
11. Salcedo PA, Lindheimer JB, Klein-Adams JC, Sotolongo AM, Falvo MJ. Effects of Exercise Training on Pulmonary Function in Adults with Chronic Lung Disease: A Meta-Analysis of Randomized Controlled Trials. *Arch Phys Med Rehabil.* 2018 Apr 17.
12. Slatore CG, Falvo MJ, Nugent S, Carlson K. Afghanistan and Iraq War Veterans: Mental Health Diagnoses are Associated with Respiratory Disease Diagnoses. *Mil Med.* 2018 May 1;183(5-6):e249-e257.
13. Gorr MW, Falvo MJ, Wold LE. Air Pollution and Other Environmental Modulators of Cardiac Function. *Compr Physiol.* 2017 Sep 12;7(4):1479-1495.
14. Falvo MJ, Serrador JM, McAndrew LM, Chandler HK, Lu SE, Quigley KS. A retrospective cohort study of U.S. service members returning from Afghanistan and Iraq: is physical health worsening over time? *BMC Public Health.* 2012 Dec 28;12:1124.

APPENDIX 3

VA's Office of Research and Development (ORD) has a number of mechanisms through which individual VA investigators or teams of investigators may apply for research funds. The Cooperative Studies Program (CSP) generally involves investigators at as few as five sites or as many as fifty sites collaborating on a single project. One such multi-site project is CSP #595:

- CSP #595: Pulmonary Health and Deployment to Southwest Asia and Afghanistan; Study Chairs: Eric Garshick, MD and Susan Proctor, DSc, Boston, MA; Paul Blanc, MD, San Francisco, CA (5/1/2016-9/30/2022): In this study, visibility data at ground level collected by the US Air Force during OEF/OIF/OND will be combined with satellite data from NASA to estimate concentrations of particulate matter (less than 2.5 microns in size) in areas where troops were located. By combining these calculations with troop location data available from the DoD, it should be possible to estimate an individual's deployment-related exposure to 2.5-micron (and smaller) particulates. Approximately 10,000 Veterans will be recruited at a total of six sites to participate in surveys and pulmonary function tests (PFTs). The results of current PFTs will be linked to each Veteran's exposure to particulate matter in the air during deployment.

VA ORD also solicits proposals from individual VA investigators for research projects related to the health of Veterans of Operations Enduring Freedom, Iraqi Freedom, and New Dawn. The "request for applications" (RFA) issued by ORD is entitled "Merit Review Award for Deployment Health Research (OEF/OIF/OND)," and it lists the health effects of burn pits as a specific area of emphasis for this research.

VA ORD is currently funding the following single-site research projects which deal with respiratory health issues in this population:

- Targeting HSC-derived Circulating Fibroblast Precursors in Pulmonary Fibrosis; Investigator: Amanda C. LaRue, PhD; Charleston, SC (10/1/2013-9/30/2018): Exposure sand and other airborne particulates cause pulmonary fibrosis (scarring) which reduces the ability of the lung to function properly, and this study is designed to determine the mechanism by which fibrosis-inducing cells develop (in mice) from hematopoietic stem cells (HSCs) and to determine if their presence can be used as an early biomarker for this condition.
- Mechanisms of Cigarette Smoke-Induced Acute Lung Injury; Investigator: Sharon Rounds, MD; Providence, RI (7/1/2015-6/30/2019): This study is designed to understand the mechanism by which acrolein, a component of cigarette smoke and burn pit smoke, damages lung cells and leads to respiratory difficulties and conditions like Acute Respiratory Distress Syndrome (ARDS) and COPD.

- Pulmonary Vascular Dysfunction after Deployment-Related Exposures; Investigator: Michael Falvo, PhD; East Orange, NJ (10/1/2017-9/30/2021): Small particulate material can deposit in the lungs and prevent the lungs from properly exchanging oxygen with the blood. In this study, gas exchange will be measured, and in cases where there is damage to the lungs, changes in blood chemistry will be monitored to develop laboratory tests that will be useful for diagnosing the condition.

Research Projects Recently Completed:

- Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans; Investigator: Rodney Schlosser, MD; Charleston, SC: Diesel exhaust particulates and other airborne hazards are known to cause oxidative inflammation in the lungs, so this study tested the efficiency of antioxidants that can be delivered to the respiratory system as nanoparticles. The tests were first conducted in cell cultures and then in mice before the next step of being developed as a treatment for Veterans.
- Effects of Deployment Exposures on Cardiopulmonary and Autonomic Function; Investigator: Michael Falvo, PhD; East Orange, NJ: OEF/OIF/OND Veterans exposed to high levels of particulate matter were subjected to an exercise challenge and then had spirometry, cerebral blood flow, blood pressure, and heart rate variability measurements made to determine the severity of their respiratory problems in this project designed to collect information that will prevent the development of chronic respiratory conditions.
- Carbon Black Induced Activation of Lung Antigen-Presenting Cells (APCs); Investigator: David B. Corry, MD; Houston, TX: Carbon black ("soot"), which collects in antigen-presenting cells (APCs) in the lung and causes inflammation, will be studied in a mouse model to determine the mechanism of the inflammation and potentially develop new ways to treat smoke-related lung damage.