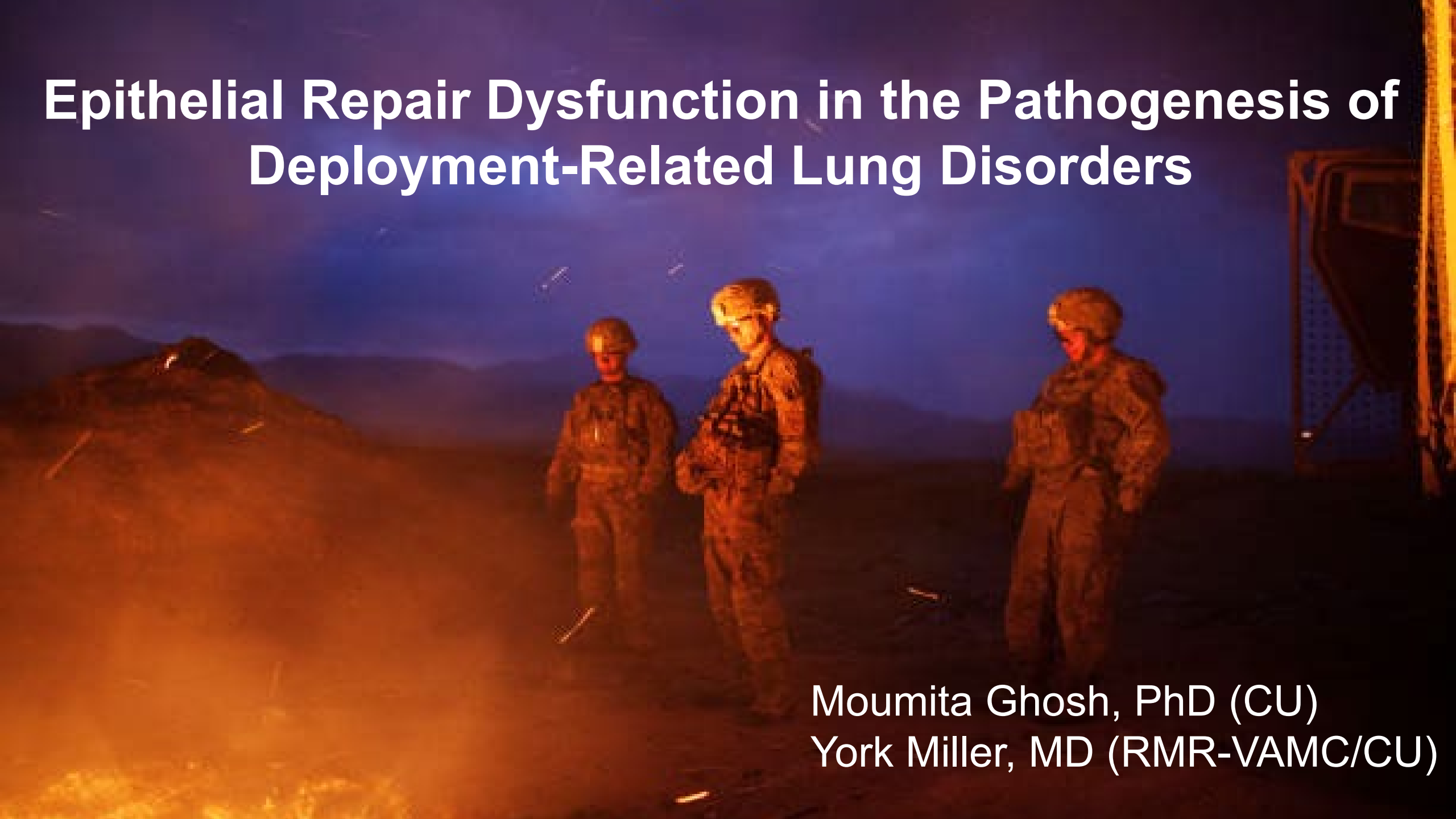
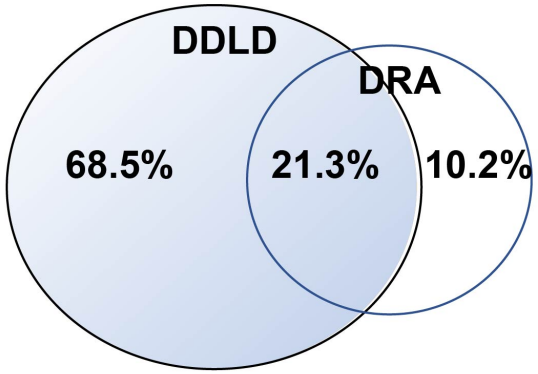
Epithelial Repair Dysfunction in the Pathogenesis of Deployment-Related Lung Disorders



Moumita Ghosh, PhD (CU)
York Miller, MD (RMR-VAMC/CU)

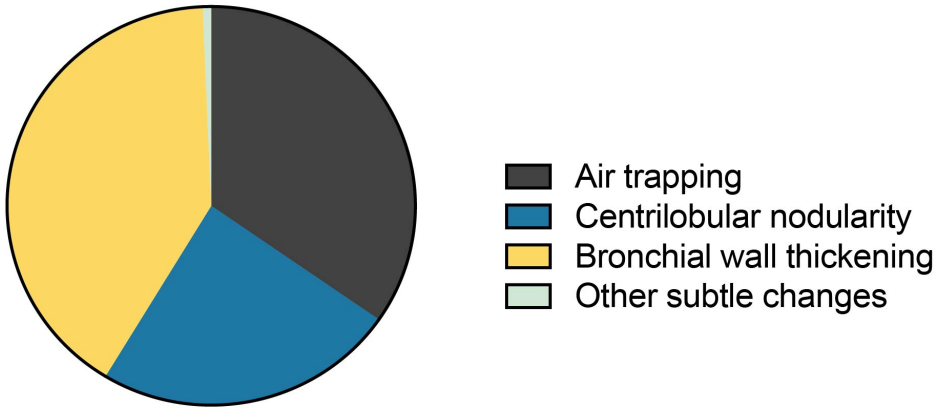
Disease Heterogeneity: A Major Issue for Diagnosis

DLD subtypes:

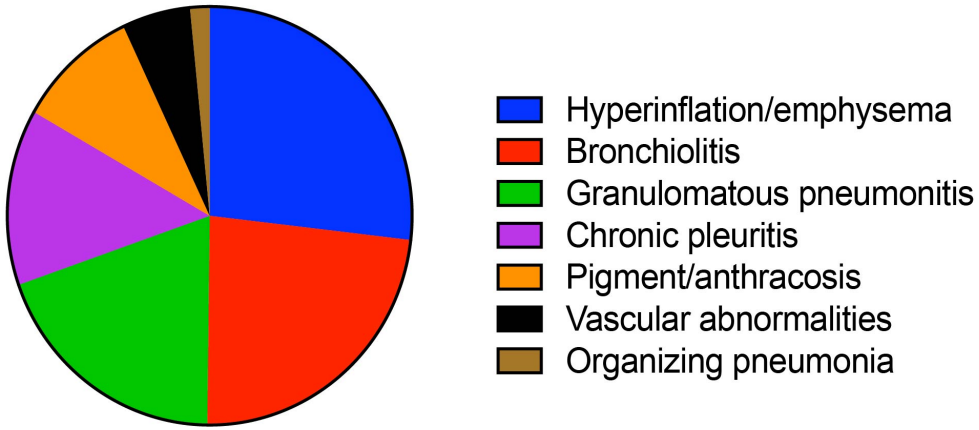


PFT is largely normal with the exception of Low Diffusion Capacity (DLCO)

DDLD heterogenity based on CT



DDLD heterogenity based on histopathology



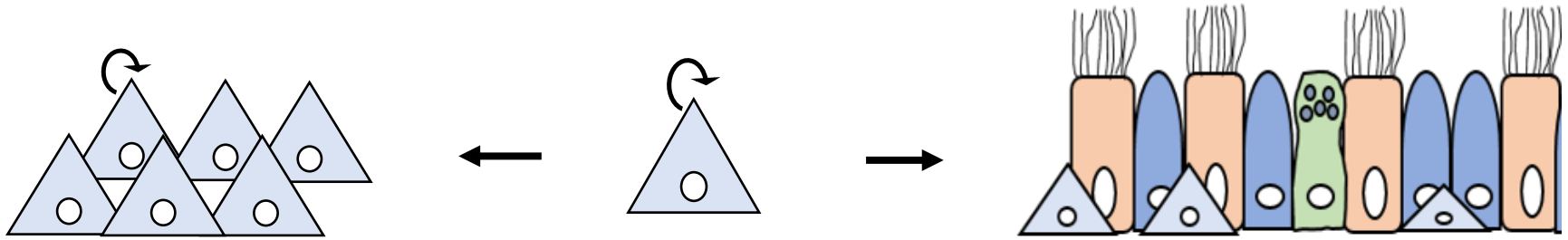
Krefft SD, et al. J Occup Environ Med. 2020

Epithelial Repair a Key Determinant of Lung Health

Epithelial Stem/Progenitor Cells

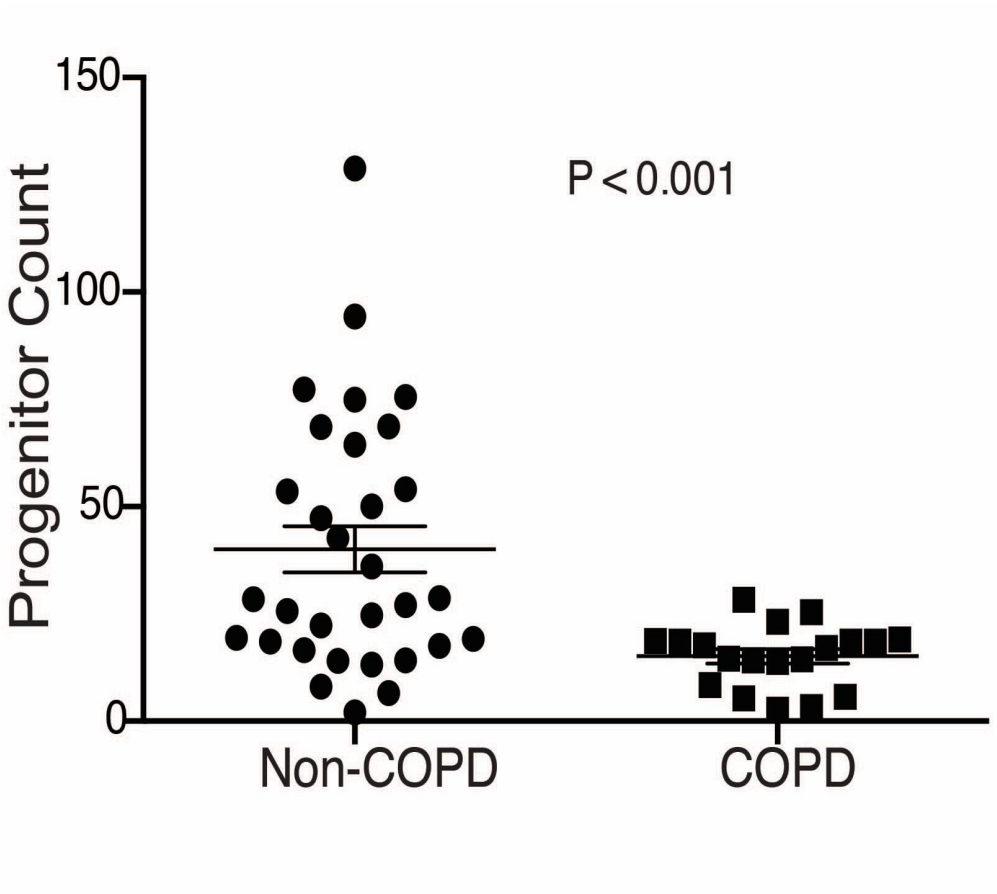
Replenish themselves
(**Self-renewal**)

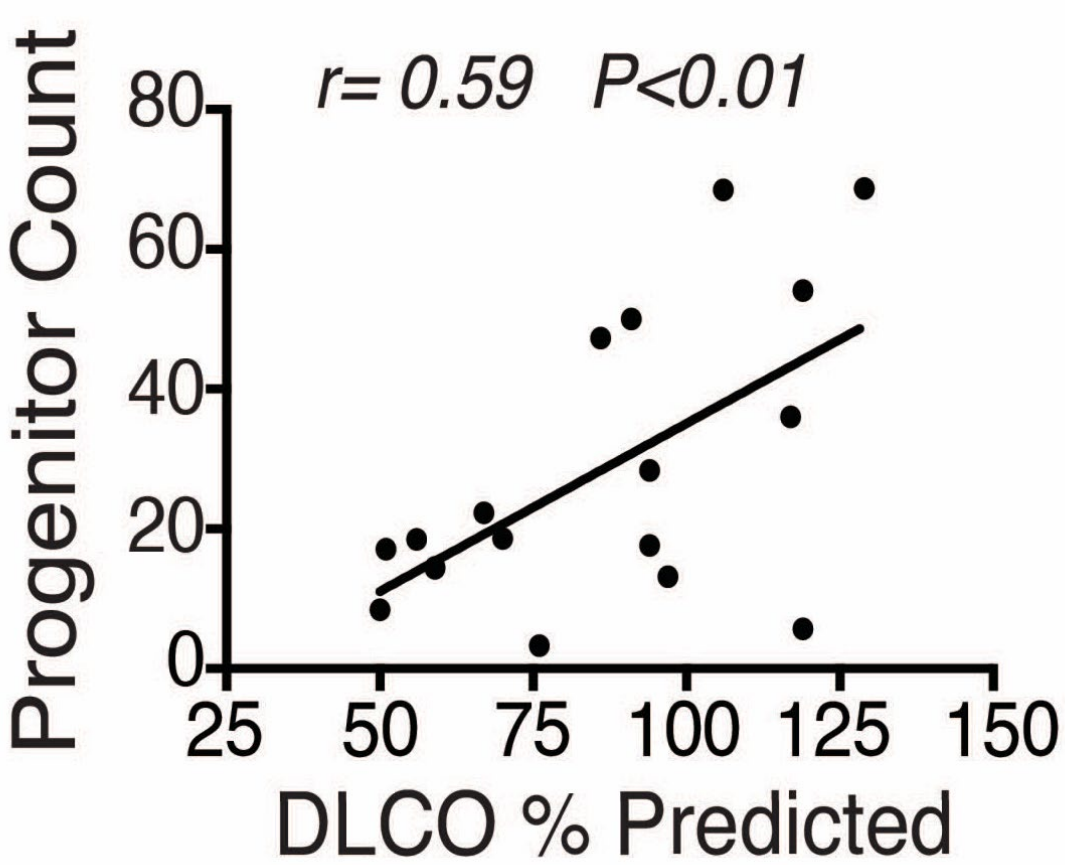
Make all cell types of the airways
(**Multipotentiality**)



Stem/Progenitor Cell

Progenitor Dysfunction in COPD

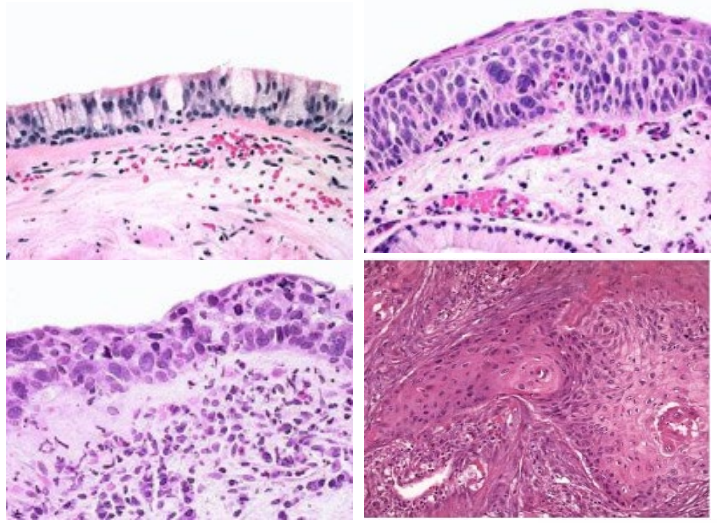




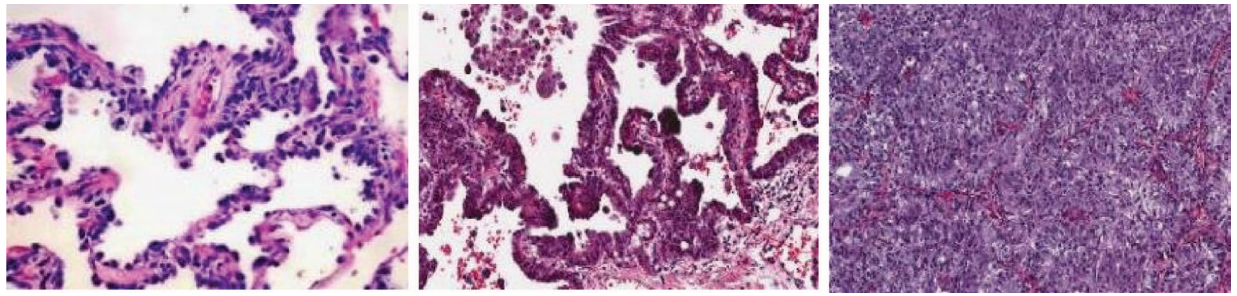
Ghosh M, et al. AJRCCM, 2018

Progenitor Dysfunction in Premalignant Lung

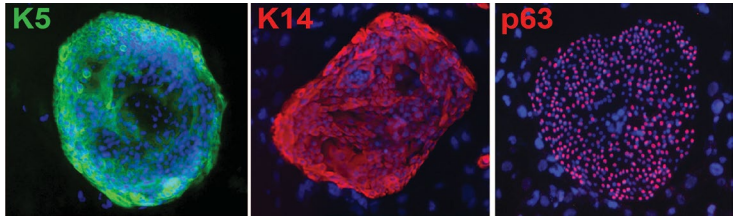
Bronchial Premalignancy: Squamous cell cancer

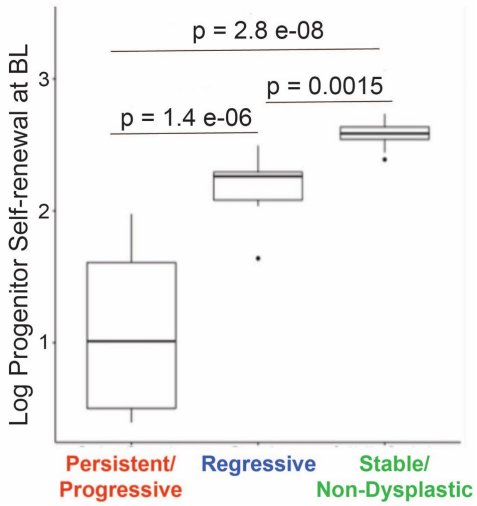


Distal lung Premalignancy: Adenocarcinoma

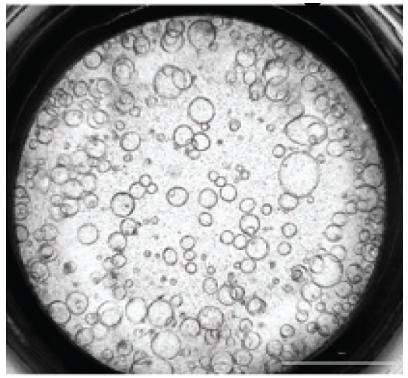


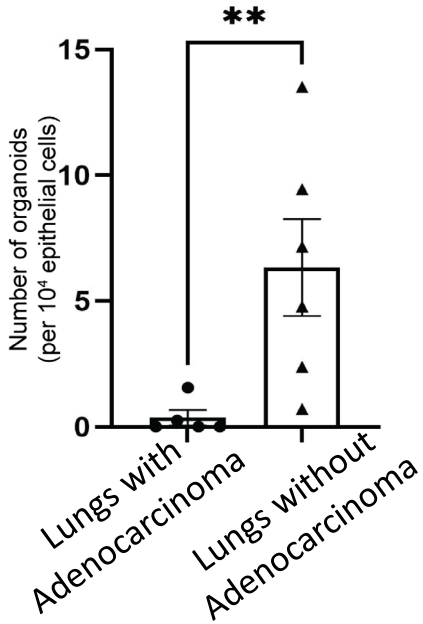
Progenitor cell clone





Lung organoid



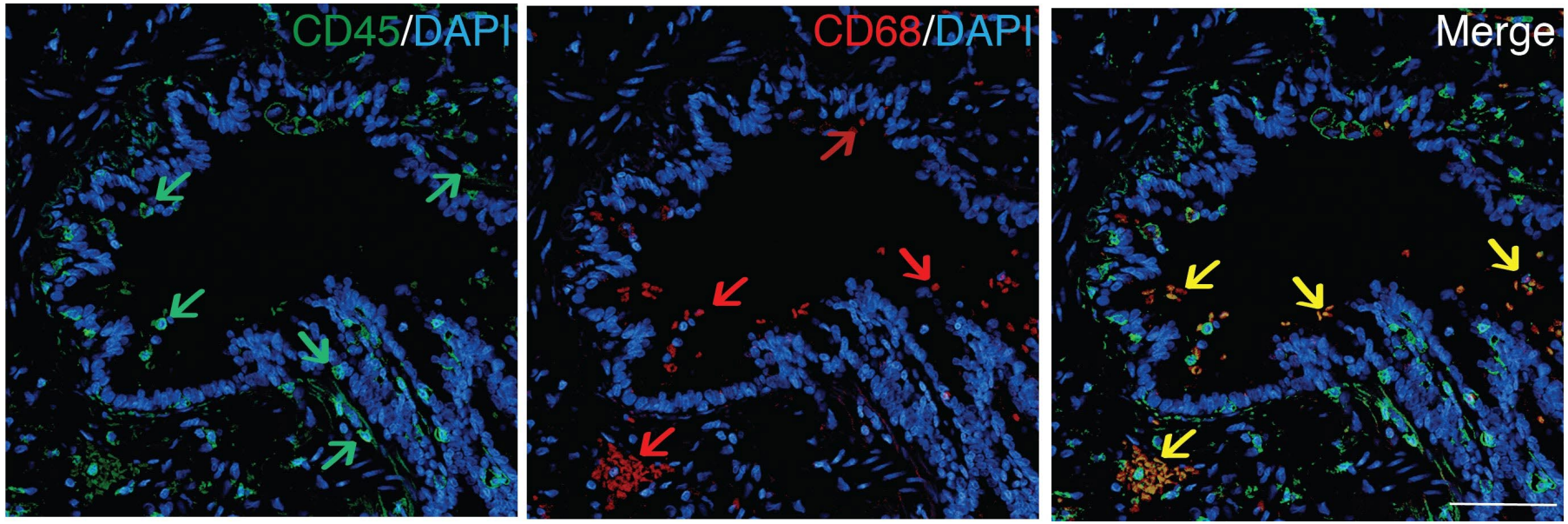


Take Home Message

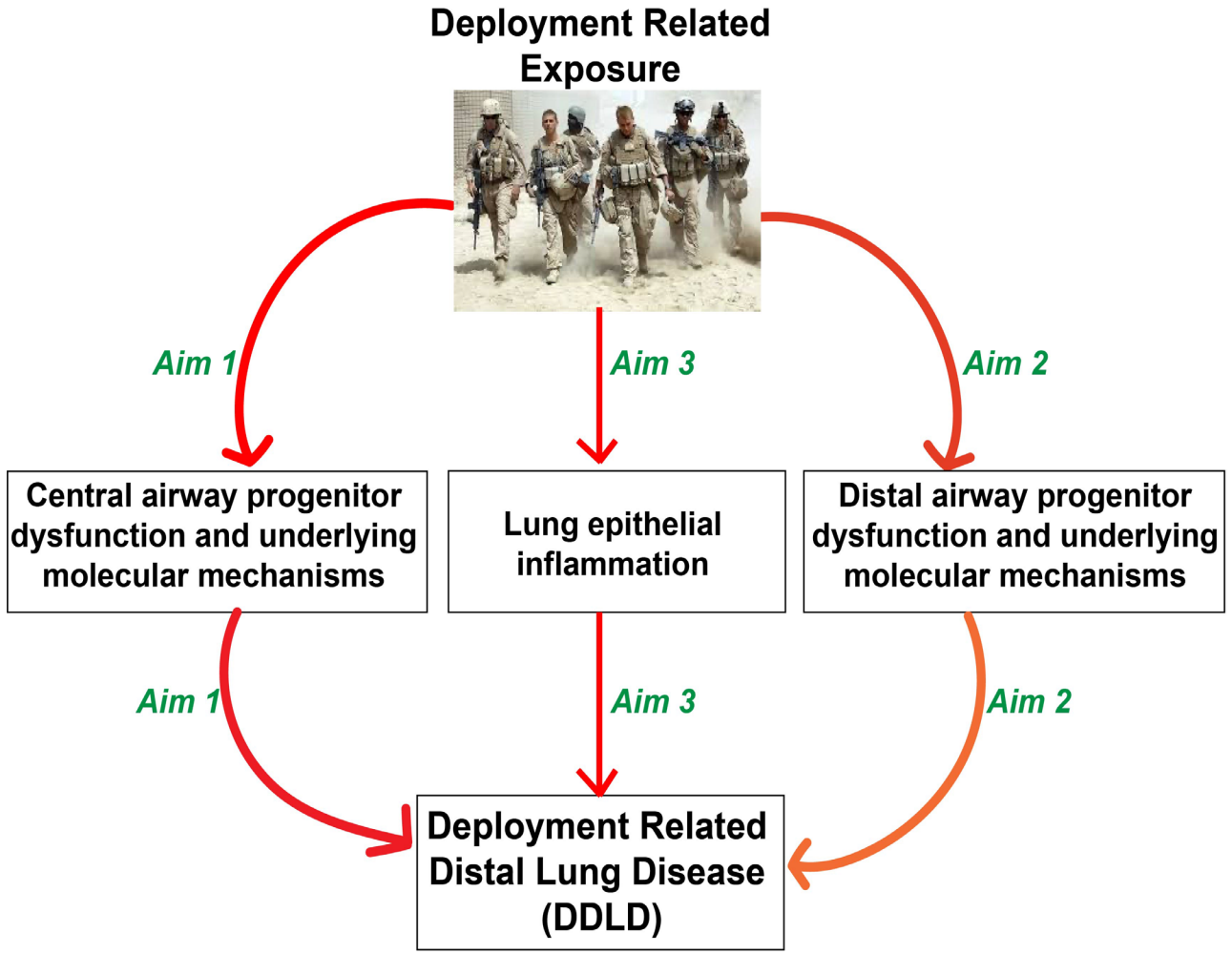
Global Dysfunction of Epithelial Progenitor Cells and Loss of Epithelial Repair Contributes To the Development of Smoking Related Lung Disease

Chronic Inflammation in Pathogenesis of DDLD

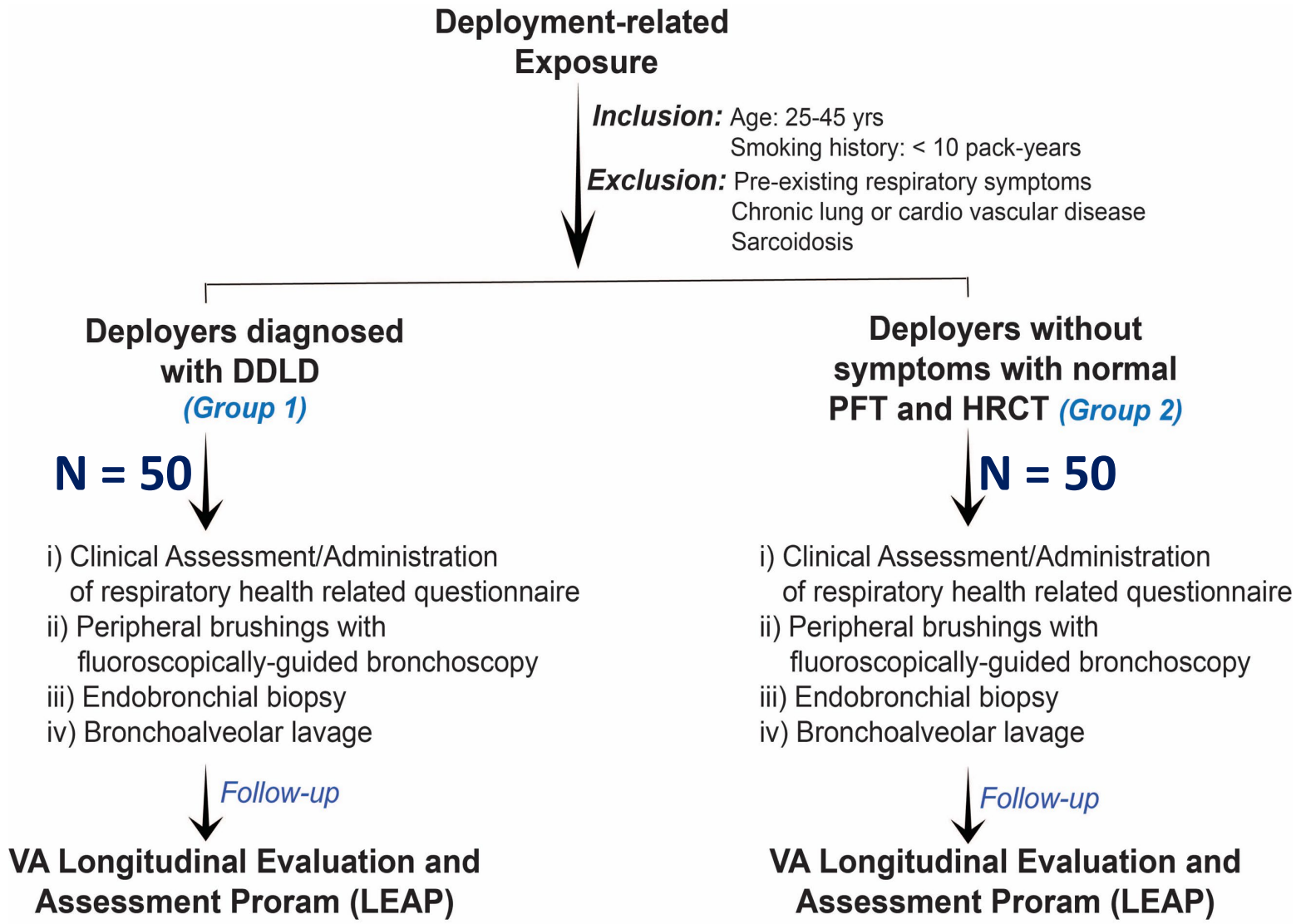
- Cell differentials in bronchoalveolar lavage ---- Variable
- Acute Eosinophilic Inflammation ---- Variable
- Mouse models exposed to desert particulate from Afghanistan (APM) --- Neutrophilic inflammation, activated monocytes
- In vitro human airway culture exposed to APM --- Type 2 immune response



Global Epithelial Dysfunction and Inflammation Contributes to DDLD Pathogenesis



Research Goals



DOD-Investigator-Initiated Translational Research Award (Ghosh/Miller)

Research Team

Core group

Moumita Ghosh, PhD
York E Miller, MD
Silpa Krefft, MD, MPH
Arnav Gupta, MD
Dexiang Gao, PhD
Daniel T Merrick, MD
Brandi Kubala, MS

Collaborators

Anisa Moore, MD
Cecile Rose, MD, MPH
Carlyne Cool, MD

CU - Core Facilities

Clinical Trial Core
Bioinformatics and Biostatistics Core
Genomics and Microarray Core
Human Immune Monitoring
Shared Resources
Flow Cytometry Shared Resources



Silpa Krefft, MD, MPH
Rocky Mountain Regional VAMC
National Jewish Health
University of Colorado

Current Clinical Research Studies in Post-Deployment Respiratory Health at VA ECHCS

Disclosures

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- Department of Defense - W81XWH-16-2-0018. Group on Lung Injury from Deployment (GLIDE) Study. Co-Investigator.
- War Related Illness and Injury Study Center (WRIISC)/VA Airborne Hazards and Burn Pit Center of Excellence (AHBPCE) – Program funding for establishment of the Post-Deployment Cardiopulmonary Evaluation Network site at the Rocky Mountain Regional VAMC.

Opinions, interpretations, conclusions and recommendations are my own and are not necessarily endorsed by the Department of Veterans Affairs or the Department of Defense.

COMIRB 19-1853: Clinical Markers and Monitoring for Post-9/11 Deployment Lung Diseases
***Longitudinal Evaluation and Assessment Program (LEAP) Study* (PI: Krefft)**

Overall Goal: development of a well-characterized cohort of Southwest Asia deployed veterans with and without lung disease

SPECIFIC AIMS:

- Aim 1: Aim 1a - Recruit and characterize a VA cohort of post-9/11 southwest Asia and Afghanistan deployment (SWAAD) veterans with and without deployment-related respiratory symptoms (DRS)/deployment-related lung disease (DLD).

- Aim 2: Characterize peripheral blood samples using Cytometry by Time-of-Flight (CyTOF) to identify cellular biomarkers of DLD and determine if there are differences in inflammation in a cohort of veterans with and without post-9/11 SWAAD DRS/DLD.

- Aim 3: Compare **longitudinal respiratory outcomes** in the established VA cohort of post-9/11 southwest Asia and Afghanistan deployment veterans with and without DRS/DLD.

LEAP

Funded by Department of Veterans Affairs

Study Protocol

CONTROLS – from VA Airborne Hazards and Open Burn Pit Registry Evaluation Clinic

Deployers without cough, wheezing, chest tightness, dyspnea (CONTROLS)

COMPLETE PERIPHERAL BLOOD DRAW, BASELINE SPIROMETRY (+DLCO in smokers), LCI TESTING, AND modified QUESTIONNAIRE

Repeat spirometry (+DLCO in smokers), LCI TESTING and QUESTIONNAIRE at a visit 15-18 months later

(n = 55)

EXCLUDED IF:
- **Alternate diagnosis (e.g. pre-deployment asthma, sarcoidosis)**
- **Lung cancer**
- **Cardiomyopathy**

Recruited from VA Chest Clinic, Chest Exposure Clinic, and Specialty Post-Deployment Cardiopulmonary Evaluation Network Clinic

Deployers with respiratory symptoms (includes those with DRA and DDLD)

COMPLETE PERIPHERAL BLOOD DRAW, BASELINE PFT, LCI TESTING, AND QUESTIONNAIRE

Repeat PFT or spirometry/DLCO, LCI testing and QUESTIONNAIRE at a visit 15-18 months later

(n = 150)

Progress to Date:

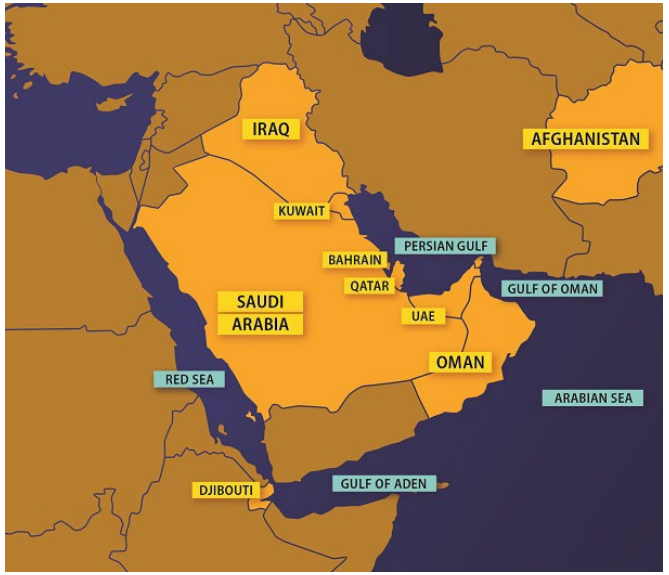
- Consented/enrolled 182 symptomatic deployers, 56 controls
- 165 completed baseline study visits
- 36 completed follow-up study visits – completed study

COMIRB 21-3104: VA Gulf War Era and Post-9/11 Southwest Asia & Afghanistan Deployment (SWAAD) Research Database and Biorepository

- Recruitment populations:
  - VA patients who served in southwest Asia (particularly those who deployed during the First Gulf War from 1990-1991 and in more recent military operations in southwest Asia and Afghanistan in the post-9/11/2001 era) as well as during peacetime operations

- Biorepository and database
  - Collect data via medical chart review and completion of questionnaires on deployment, military and medical history (REDCap database)
  - Peripheral blood sample to be banked for future research
  - Enrolling study participants currently, symptomatic and healthy veterans

- PI: Silpa Krefft, Co-Investigators: Arnav Gupta, Alison Wilczynski
- Number of study participants: Up to 5000 eligible veterans



Funded by Department of Veterans Affairs

COMIRB 21-2804: Study to Improve Deployment Related Asthma by Using L-Citrulline Supplementation (SEALS)

PIs: Fernando Holguin (CU), Cecile Rose (NJH); Silpa Krefft (VA Site Leader)

- Substantial number of veterans with deployment-related asthma (DRA) have non-Th2 (or Th2)-low asthma endotype.
- Novel therapies are needed for non-Th2 asthma.

- Clinical trial (multi-site at CU/NJH/VA) with target enrollment of 75 study participants (veterans with DRA from First Gulf War era through the post-9/11 era) over the next 4 years
  - Actively recruiting/enrolling now

- Project Aims of phase II proof of concept study are to demonstrate the efficacy and safety of L-citrulline supplementation, in addition to asthma controller medications, for improving the following in those with deployment-related asthma (DRA):
  - Asthma control
  - FeNO
  - Lung function

Funded by Department of Defense

COMIRB 22-2069: High-Intensity Interval Training (HIIT) to Improve the Symptoms of Deployment-Related Respiratory Disease (DRRD)

- ~50% of participants with DRRD (asthma and/or distal lung disease/small airways disease such as bronchiolitis) demonstrate reduced VO2max
- In this pilot study, we will study 12 veterans with DRRD
  - Echocardiography, venous metabolomics, and cardiopulmonary exercise testing (CPET) before and after a 12-week high-intensity interval training exercise intervention
  - Generate pilot data regarding impact of HIIT on cardiopulmonary performance and its efficacy in improving functional capacity and symptoms in deployment-related respiratory disease
- Patient enrollment: May 2023 – October 2023
- **PI: Lindsay "Shelley" Forbes, MD**
- Co-Investigators: William Cornwell, MD, MSCS; Silpa Krefft, MD, MPH
- Funded by: VA Airborne Hazards and Burn Pit Center of Excellence (AHBPCE) Pilot Project Research Award FY2023-001

COMIRB 23-0260: Mitochondrial Injury in Peripheral Blood Mononuclear Cells in Deployment-Related Lower Respiratory Disease (PI: Arnav Gupta, MD)

Background: Particulate exposures may cause DNA damage through generation of reactive oxygen species, and increased mtDNA injury has been associated with mitochondrial dysfunction.

Objective: Conduct a more detailed investigation into mitochondrial function and mtDNA lesions in PBMCs from Veterans with deployment-related lung disease (DLD).

Aim 1: Identify changes in the mitochondrial oxygen consumption rate in PBMCs obtained from patients with deployment-related lung disease (DLD) that includes asthma and deployment-related distal lung disease.

- *Hypothesis:* Mitochondrial dysfunction, evidenced by a decrease in mitochondrial respiration, is a pathologic feature of PBMCs obtained from patients with DLD.
- *Approach:* Measure **extracellular acidification rate** and oxygen consumption rate using the **Agilent Seahorse XF** assay in PBMCs obtained from 10 veterans with DLD and 10 deployed healthy controls.

Aim 2: Demonstrate an increased burden of mtDNA lesions and increased mtDNA copy number in PBMCs obtained from patients with DLD.

- *Hypothesis:* mtDNA from patients with DLD will exhibit a greater burden of mutations and per-cell copy number compared with controls.
- *Approach:* Quantify **mtDNA lesions** and copy number per cell using quantitative PCR-based assays in 10 veterans with DLD and 10 controls.

Funded by: VA Airborne Hazards and Burn Pit Center of Excellence (AHBPCE) Pilot Project Research Award

Acknowledgements

Rocky Mountain Regional VAMC/VA Eastern Colorado HCS
- Arnav Gupta, MD (Co-Investigator, Clinician)
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