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AWARD NUMBER: W81XWH-17-1-0575

TITLE: Identifying Novel Immune and Radiographic CT Imaging Signatures of Chronic Bronchiolitis

PRINCIPAL INVESTIGATOR: John J Osterholzer

RECIPIENT: University of Michigan
Ann Arbor, MI 48109

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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT
Soldiers returning from deployment to South West Asia commonly report new respiratory symptoms. Inhalational lung injuries from respiratory toxins are suspected and we hypothesize that these toxins injury airway club cells and result in chronic bronchiolitis which is characterized by a persistently abnormal immune response and scarring within small airways. In this funding period, we have shown that specific and repetitive club cell injury in mice results in chronic bronchiolitis as evidenced by weight loss, airway thickening, increased lung collagen deposition, and an accumulation of alternatively-activated lung macrophages. Efforts to identify potential biomarkers of chronic bronchiolitis present in the lung lavage fluid or peripheral blood are in progress. We have also achieved numerous administrative requirements so that we can begin to determine whether parametric response mapping, a novel CT analytical technique, can identify airway abnormalities on CT scans obtained from a cohort of symptomatic Gulf War Veterans evaluated at the Airborne Hazards Clinic of Excellence located in the New Jersey War Related Illness and Injury Study Center.

15. SUBJECT TERMS
lung; injury; airway; toxin; epithelium; bronchiolitis; club cell; macrophage; monocyte; cytokines; chemokines; mice; radiographic; ct-scan; tomography

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TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

   Soldiers returning from deployment to South West Asia during the First Gulf War and Operations Enduring Freedom/Iraqi Freedom/New Dawn commonly report new respiratory symptoms including dyspnea on exertion, cough, and chronic fatigue. Inhalational lung injuries are suspected given the multiple exposures to potential respiratory toxins present in these deployment zones. Our proposal highlights numerous lines of evidence suggesting that these toxins injury airway club cells and cause chronic bronchiolitis which is characterized by a persistently abnormal immune response and scarring within small airways (the bronchioles) that results in many of the respiratory symptoms soldiers experience years after deployment. The first objective of this research is to study common injury patterns that result from repetitive club cell injury in mice in an attempt to identify potential biomarkers of chronic bronchiolitis present in the lung lavage fluid or peripheral blood. The second objective is to determine whether impairing the accumulation of lung monocytes and macrophages (in mice) can protect against chronic bronchiolitis. The third objective is to determine whether parametric response mapping, a novel CT analytical technique, can identify airway abnormalities on CT scans obtained from a cohort of symptomatic Gulf War Veterans evaluated at the Airborne Hazards Clinic of Excellence located in the New Jersey War Related Illness and Injury Study Center.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

   lung; injury; airway; toxin; epithelium; bronchiolitis; club cell; macrophage; monocyte; cytokines; chemokines; mice; radiographic; ct-scan; tomography

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

   What were the major goals of the project?

   1. Specific Aim 1: To define the pathogenesis and local and systemic immune signatures of CB.

   2. Specific Aim 2: To determine whether the development of CB is CCR2-dependent and directly attributable to the recruitment and differentiation of Ly-6Chigh monocytes.

   3. Specific Aim 3: To determine whether CT-based parametric response mapping (PRM) can identify a unique radiographic signature in former soldiers with Gulf War Illness (GWI).

   What was accomplished under these goals?

   1. Administrative. All requisite administrative goals were accomplished in year 1 as outlined in last year's Annual Report. This year, we have submitted all required renewal reports required to remain in compliance with The University of Michigan, the VA Health Care System, and those required by the Department of Defense.

2. Animal Research

Specific Aims 1 and 2: We are now very adept at breeding the triple transgenic strain of "CC-DTA" mice and appropriate littermate controls required for our experiments. Data obtained in the preceding cycle demonstrated that repetitive diphtheria toxin mediated club cell injury results in weight loss, increase cellular apoptosis, and collagen accumulation. We also demonstrated that club cell injury is associated with an accumulation of: a) total CD45+ leukocytes; b) alveolar macrophages; and c) exudate macrophages; lung macrophages show evidence of increased CD206 expression providing important evidence that they are alternatively (M2) activated in keeping with our hypothesis.

Additional analysis revealed that club cell injury is associated with a significant accumulation of eosinophils and CD8+ T cells whereas we did not observe increased accumulations of the following leukocytes subsets: CD103+ and CD11b+ conventional DC, monocyte-derived DC, neutrophils, or CD4+ T cells. Histology performed on these mice confirmed the presence of chronic bronchiolitis as evidenced by epithelial thinning associated with chronic immune infiltrates in the subepithelial regions.

In this funding cycle, we have extended our findings to show that following club cell depletion, we see an increase in cell death/apoptosis (by caspase assay (Fig 1) with a subsequent decline in club cells (cells expressing SCGB1A1/CCSP; note that club cells recover by D2 (Fig 2) and yet fibrosis persists (see below).

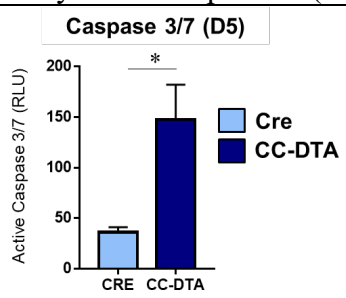


Fig 1: Whole lung active caspase 3/7 at D5

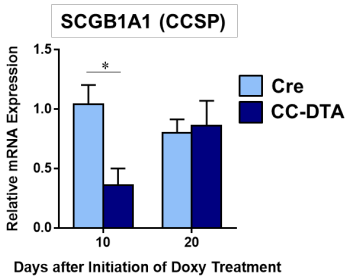


Fig 2: Whole lung gene expression (by qRT-PCR) for SCGB1A1 (CCSP)

We've also shown that the club cell depletion and airway fibrosis in mice recapitulates that seen in soldiers (Fig 3) and we confirm that club cell depletion in mice increases lung collagen content (by collagen gene expression (Fig 4) and hydroxyproline assay (Fig 5).

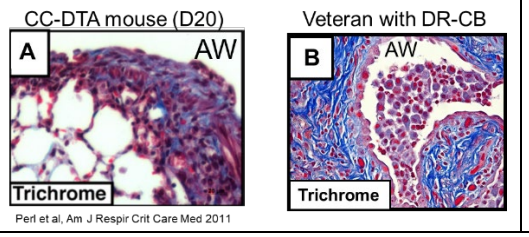


Fig 3. Collagen staining (in blue) shows airway fibrosis in CC-DTA mice and a Veteran with DR-CB

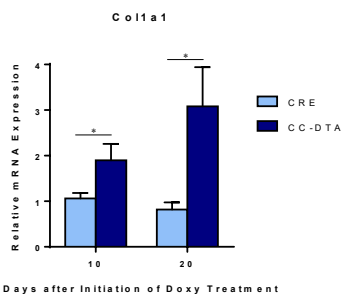


Fig 4. Whole lung gene expression (by qRT-PCR) for Col1a1 at D20

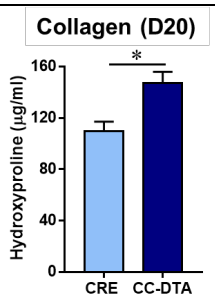


Fig 5. Lung collagen content (by hydroxyl-proline assay) at D20

We then extensively examined the immune cells recruited to the lung in response to airway injury. Results show accumulations of a substantial number of alveolar macrophages with smaller increases observed for eosinophils, Ly-6C high monocyte, monocyte-derived DC, and exudate macrophages (Fig 6).

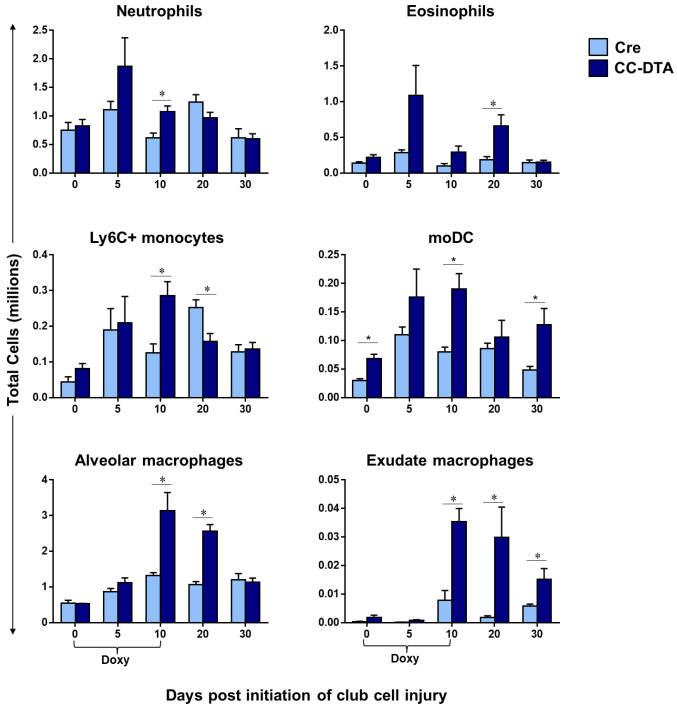


Fig 6. Accumulation of lung myeloid cells in response to club cell injury as identified using flow cytometric analysis.

We also show that club cell injury and leukocyte accumulation is associated with an increase in markers of oxidative stress, IL-10, and alternative macrophage activation (Fig 7).

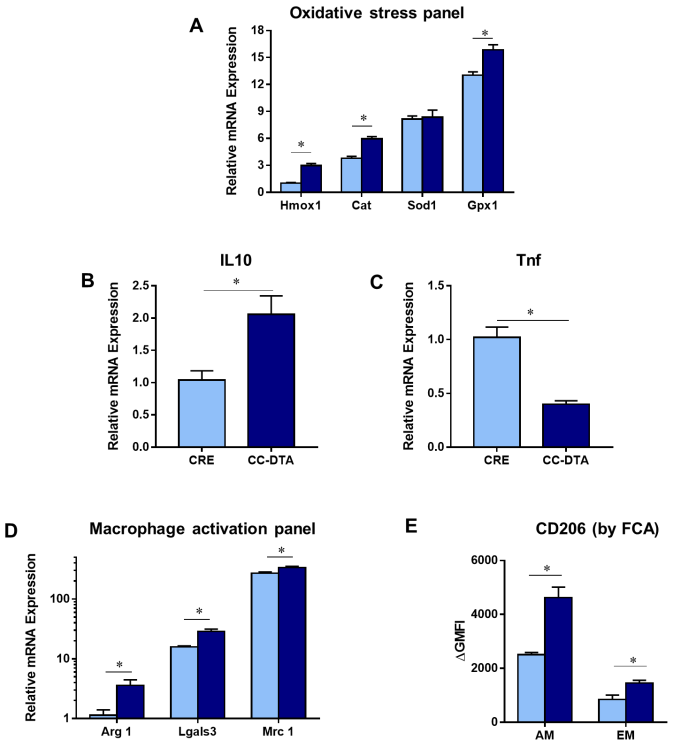


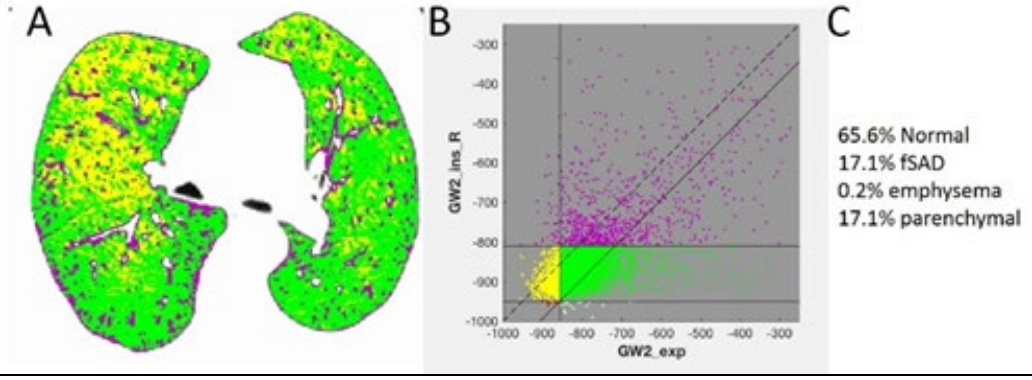
Fig 7. CC-DTA and Cre (littermate control) mice on protocol (per Methods). Whole lung gene expression (by qRT-PCR) at protocol D20 for genes associated with oxidative stress including Hmox1 (heme oxygenase), Cat (catalase), Sod1 (superoxide dismutase), and Gpx1 (glutathione peroxidase) (A); cytokines including Il10 (IL-10) (B), and Tnf (TNFa) (C); and genes associated with alternative macrophage activation including Arg1 (arginase), Lgal3 (galectin 3), and Mrc1 (mannose receptor/CD206) (D). Change in mean fluorescence intensity for anti-CD206 antibody staining as detected by FCA on alveolar macrophages (AM) and exudate macrophages (EM) identified (per Fig. 5) at protocol D20. * $p < 0.05$ by unpaired student t-test from n = 5 mice per cohort.

Having completed our thorough immunophenotyping of mice with specific club cell injury, we are not well-positioned to begin experiments in which airway injury is induced by sulphur dioxide exposure and further assess the effects of anti-CCR2 blockade (Aim 2). We are awaiting the acquisition of several pieces of equipment and the anti-CCR2 antibody that will allow us to being these experiments.

Collectively, experiments outlined in Aims 1 and 2 are approximately 60% complete and are progressing as planned. Portions of this work were presented last May at the 2019 International Conference of the American Thoracic Society. Manuscript preparations are underway and additional data will be presented at the 2020 International Conference of the American Thoracic Society.

Human research (Aim 3). The objective of this research was to obtain high resolution CT (HRCT) scans from Gulf War veterans with respiratory complaints and to analyze them using CT-parametric response mapping (PRM) for evidence of radiographic abnormalities indicative of chronic lung disease. PRM requires a set of paired, volumetric, inspiratory and expiratory HRCTs. In the first year, we overcame a set of administrative challenges during the first funding cycle and began transferring CT scans from the New Jersey VA to the University of Michigan. In the past year, 8 scans were obtained at the NJ-VA from veterans who had served in the GW and who had concerns about deployment-related health. Seven scans were sent to the University of Michigan beginning last winter and all seven have been analyzed by Dr. Galban. As was documented in additional correspondence sent to the DOD, in June it was noted that the 8th CT scan prepared for transfer was stripped of all unique identifiers with the exception of a date of birth. The prior 7 scans were re-reviewed. The first scan had been stripped of all identifying information whereas scans 2-7 contained the DOB. We have alerted the institutions and the DOD and have since provided documentation of our response, some of which is ongoing. As a result, we have not sent additional scans although Dr. Falvo's group at the NJ-VA continues to see veterans with GWVI and we will resume sending scans once all approvals have been obtained.

We do have proof of concept analysis of one of our first cases from a symptomatic Gulf War Veteran evaluated at the NJ-WRIISC whose CT was analyzed by Dr. Galban. These results suggest a decrease in normal lung tissue (66.6%) and an increase in functional small airways disease (17.1%) in this individual (Fig. 8).



PRM results obtained on a symptomatic GW Veteran showing spatial (A), graphic (B), and actual (C) PRM data depicting 65.5% normal lung (green), 17.1% functional small airways disease (fSAD; yellow), 0.2% emphysema (red), and 17.1% parenchymal disease (purple).

From an analysis perspective, once we resume sending scans, Dr. Galban can analyze the HRCT in batched fashion such that the PRM analytic step will not be rate-limiting in the future.

3. **What opportunities for training and professional development has the project provided?**

Nothing to report.

How were the results disseminated to communities of interest?

The data from our murine model outlined above was presented at the International Conference of the American Thoracic Society in May of 2019. Updated data sets from ongoing experiments will be completed by October 31st 2019 in time for the preparation and submission of an abstract to the meeting in May of 2020. Also in this funding cycle, we presented our preliminary results using PRM to analyze a subset of OEF-OIF soldiers seen by Dr. Miller at the VUMC. This data, presented at the International Conference of the American Thoracic Society in May of 2019, showed evidence of increased function small airways in soldiers with biopsy evidence of chronic bronchiolitis. We anticipate this data will inform our current and similarly structured study looking for evidence of chronic bronchiolitis or other forms of deployment-related lung disease in GW Veterans. I was able to share some of these ideas and this preliminary data on a conference call organized by the Department of Veterans Affairs for investigators interested in studying Gulf War Illness. We have tentative plans to present some preliminary results of our studies on scans obtained from GW Veterans at the International Conference of the American Thoracic Society in May of 2020.

What do you plan to do during the next reporting period to accomplish the goals?

As discussed above, plans for the next reporting period pertaining to our studies on murine chronic bronchiolitis include: 1) Complete our data analysis on samples collected from injured CC-DTA mice and uninjured control wild type mice at the D5, D10 and D20 timepoints; 2) Repeat experiments to verify reproducibility and to attain sufficient numbers of samples to strengthen the statistical analysis; 3) Initiate experiments using the sulphur dioxide exposure model of chronic bronchiolitis and begin to compare and contrast results obtained from both experimental models; and 4) Initiate experiments testing whether treatment of mice with anti-CCR2 blocking antibody will reduce macrophage accumulation and improve chronic bronchiolitis is response to selective club cell injury or sulphur dioxide exposure. We are currently preparing our first scientific manuscript describing our findings.

Plans for the next reporting period pertaining to our human studies are focused on resuming the transfer of HRCT scans performed for clinical indications on GW veterans seen at the AHCE/NJ-WRIISC and having them properly de-identified and sent to the UM for PRM analysis. We are positioned to present some preliminary findings at the ATS conference (described above).

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Our published abstract and poster presentation is the first to show that repetitive and selective club cell injury results in airway fibrosis that is associated (and preceded by) oxidative stress and an accumulation of alternatively activated (M2) macrophages that display a profibrotic phenotype.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
We are now using a NIH, Clinical Trials Application software program and a second layer of confirmation by research personnel at the New Jersey VA to ensure that CT scans are properly de-identified prior to transfer to the University of Michigan.

Actual or anticipated problems or delays and actions or plans to resolve them

We believe we have adequately resolved the CT-de-identification problem and are awaiting final approvals from the University of Michigan and the DOD to resume sending scans. We do not believe this will ultimately impact our ability to obtain an adequate cohort of scans that we can analyze in an expedited manner thereafter.

Changes that had a significant impact on expenditures

We had budgeted approximately $70,000 a year towards 90% of the salary of a research scientist in my lab at the AAVAHS. However, due to a budgetary surplus at the NJ- VA/WRIISC, they had generously agreed to pay this salary in full from 9/17 through 8/18. This one-time arrangement expired 8/31/2018. Thereafter, additional funds in support of our research scientist's salary this fiscal year were provided by the Department of Veterans Affairs in response to a request for bridge funding while my VA Merit Award Proposal was under review. Thus, our overall expenditures are lower than expected at this point in our study.
Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

We are using an NIH program to de-identify CT scans (as above); no other changes in the use or care of human subjects.

Significant changes in use or care of vertebrate animals

There have been no significant changes.

Significant changes in use of biohazards and/or select agents

There have been no significant changes.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications.

  None

  Books or other non-periodical, one-time publications.

  None.

  Other publications, conference papers and presentations.

  An abstract describing our murine model was presented at the International Conference of the American Thoracic Society in May of 2019 and published in the American Journal of Pulmonary and Critical Care Medicine: "Murine Modeling of Deployment-Related Chronic Bronchiolitis by Conditional Depletion of Airway Club Cells"; J.J. Osterholzer, S. Teitz-Tennenbaum, S.P. Viglianti, A.M. Jomaa, A.-K.T. Perl; American Journal of Respiratory and Critical Care Medicine 2019;199:A2836. See appendix 1

  A second abstract describing our work using CT-PRM to evaluated for functional small airways disease was also published in the same journal: "Parametric Response Mapping Identifies Increased Functional Small Airways Disease in Soldiers with Biopsy Evidence of Chronic Bronchiolitis"; J. J. Osterholzer, A. R. Guttentag, R. F. Miller, M. J. Falvo, C. J. Galban; American Journal of Respiratory and Critical Care Medicine 2019;199: A4256. Although this abstract did not specifically involve studies obtained on Gulf War Veterans, it provides evidence of our capabilities to successfully perform this analysis. See appendix 2.

- **Website(s) or other Internet site(s)**

  None.

- **Technologies or techniques**

None.

- **Inventions, patent applications, and/or licenses**

  None.

- **Other Products**

  None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

1. Name: John Osterholzer
   a. Project Role: PI
   b. ORCID ID: 0000-0002-7332-2348
   c. Nearest person month worked: 3
   d. Contribution to Project: As the PI, I am overseeing all aspects of the research including the animal subject research being performed in my laboratory and the human subject research that is being coordinated with my primary collaborators (Craig Galban; University of Michigan and Michael Falvo; New Jersey VA Medical Center/WRIISC). My duties include data analysis, abstract, presentation, and manuscript preparation, and oversight and/or maintenance of all requisite approvals pertaining to our animal and human research.
   e. Funding Support: As provided by this award.

2. Name: Michael Falvo
   a. Project Role: Co-I
   b. Nearest person month worked: 1
   c. Contribution to Project: Dr. Falvo contributes to the acquisition of CT scans from the New Jersey VA WRIISC and their transfer to Dr. Galban at the University of Michigan. He assists with experimental design, data analysis, and manuscript preparation. He also assists with maintaining local compliance with IRB requirements.
   d. Funding Support: As provided by this award.

3. Name: Craig Galban
   a. Project Role: Co-I
   b. Nearest person month worked: 1

c. Contribution to Project: Dr. Galban contributes to the analysis of CT scans obtained from the New Jersey VA WRIISC. He assists with experimental design, data analysis, and manuscript preparation.
d. Funding Support: As provided by this award

4. Name: Name: Duncan Ndirangu
    a. Project Role: Research coordinator
    b. Nearest person month worked: 1
    c. Contribution to Project: Duncan assists Michael Falvo at the New Jersey VA WRIISC in the acquisition of CT scans from the New Jersey VA WRIISC and their transfer to Dr. Galban at the University of Michigan. He also assists with maintaining local compliance with IRB requirements.
    d. Funding Support: As provided by this award.

5. Name: Name: Seagal Teitz-Tennenbaum
    a. Project Role: Research Laboratory Specialist Intermediate
    b. Nearest person month worked: 9
    c. Contribution to Project: Seagal set up and performed all animal experiments involving the collection and analysis of histologic and morphometric data as outlined in this proposal.
    d. Funding Support: We were able to obtain additional funding for Seagal's salary via a Bridge Funding mechanism through the Department of Veterans Affairs.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

1. Name: John Osterholzer
    a. Role: PI
    b. Change in other support: I re-submitted (3/2019) a new VA Merit Award entitled "Advancing Non-Invasive Diagnostics and Treatments of Deployment-Related Chronic Lung Disease in Gulf War Veterans." This grant was selected for funding pending completion of my Just In Time Documents. The scientific experiments proposed will advance, but do not overlap, with the currently funded DOD award. My proposed effort on this award is 4 months.

2. Name: Michael Falvo
    a. Role: Co-I
    b. Change in other support: Dr. Falvo has is a Co-Investigator on the VA Merit Award described above for Dr. Osterholzer. Dr. Falvo has effort on grants pending as detailed in his OS page, including: "Lung Injury Etiology, Risk Factors, and Morbidity of Single and Repeated Low-Level Blast Overpressure Exposure" (DOD), and "Burn Pit Exposure and Post-Deployment Dyspnea" (DOD). The experiments

proposed in these two grants do not overlap with the currently funded DOD award. He reports no overlap between these studies and the current grant.

3. Name: Craig Galban
    a. Role: Co-I
    b. Change in other support: Dr. Galban Dr. has is a Co-Investigator on the VA Merit Award described above for Dr. Osterholzer. The experiments proposed in these two grants do not overlap with the currently funded DOD award. Dr. Galban has also secured funding on several additional grants as detailed in his Other Support. These include " Commercialization of a CT-based Technique for BOS Assessment" (Imbio/NIH) and "An Early Imaging Marker of Emphysema" (NIH). He has grants pending including: " Parametric Response Mapping-Guided Analysis of Small Airway Pathology in COPD" (NIH), "Prediction of COPD Progression by PRM" (NIH), "Understanding the Origins of Early COPD" (NIH), "Parametric Response Mapping to Detect and Endotype CLAD" (CF Founation), " : Parametric Response Mapping-Guided Analysis of Small Airway Pathology in COPD" (NIH), and "Personalized Radiation Therapy in Lung Cancer: Minimizing Cardiac and Lung toxicity via a Utility Approach" (NIH). He reports no overlap between these studies and the current grant.

What other organizations were involved as partners?

1. Organization name: The VA Ann Arbor Medical Center
    a. Organization location: Ann Arbor, Michigan
    b. Partner's contribution to the project: The VAAAMC is the site of Dr. Osterholzer's office and laboratory and also contains the animal care facility used to house the mice used in the animal studies described in the proposal. Thus, this facility provides significant space and indirect infrastructure that supports our studies. Their animal care, biosafety, and IRB committees have also provided additional oversight.

2. Organization name: The VA New Jersey Medical Center and War Related Illness and Injury Study Center
    a. Organization location: East Orange, New Jersey
    b. Partner's contribution to the project: The VANJMC is the site of the WRIISC which evaluates Gulf War era veterans in the Airborne Hazards Clinic of Excellence under the direction of Dr. Michael Falvo (Co-I). Dr. Falvo and his staff assure that high resolution CT scans obtained on these veterans for clinical purposes are subsequently de-identified and transferred to Craig Galban (Co-I) at the University of Michigan. Thus, this facility provides significant clinical and office space and additional indirect infrastructure (including the CT scanners) that support our studies. Their biosafety and IRB committees have also provided additional oversight.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

We have attached our abstract from our presentation at the 2019 International Conference of the American Thoracic Society which reports our data obtained using our murine model of club cell injury.

Print this Page for Your Records Close Window

Control/Tracking Number: 2019-S-11718-ATS
Activity: Scientific Abstract
Current Date/Time: 10/30/2018 2:41:54 PM

Murine Modeling of Deployment-Related Chronic Bronchiolitis by Conditional Depletion of Airway Club Cells

Author Block: J. J. Osterholzer[1], S. Teitz-Tennenbaum[2], S. P. Viglianti[1], A. M. Jomaa[1], A. T. Perl[3];
[1]Pulm Div 111G, Ann Arbor VA and University of Michigan Health System, Ann Arbor, MI, United States, [2]Internal Medicine, University of Michigan, Ann Arbor, MI, United States, [3]Cincinnati Childrens Hosp Med Ctr, Cincinnati, OH, United States.

Abstract:
RATIONALE: A subset of soldiers deployed to southwest Asia develop deployment-related chronic bronchiolitis (DR-CB) characterized by persistent inflammation and airway fibrosis. Inhalational insults from respiratory toxins are suspected, yet the inciting agents and resultant pathophysiology that develops following exposures are poorly understood. No treatments for DR-CB have been identified. We hypothesize that injury to club cells, critical progenitor cells located within the airway epithelium, represents a common injury pathway central to the development of DR-CB. To better understand this pathway, we characterized the cellular immune response in transgenic mice subjected to selective and sustained club cell depletion to identify cellular and molecular mechanisms that may prove critical to the development of persistent inflammation and peribronchiolar fibrosis.
METHODS: To model chronic bronchiolitis, we used inducible triple transgenic CC-DTA mice that express diphtheria toxin A only within club cells (in response to doxycycline). CC-DTA and single transgenic litter-mates control mice received doxycycline for 10 consecutive days. Weight curves were generated and lungs, harvested at day 0, 5 and/or 20 of this protocol, were analyzed for: 1) Histopathology; 2) Apoptosis by active caspase 3/7 assay; 3) Fibrosis by hydroxyproline content and Masson's trichrome staining; 4) Leukocyte subpopulations by fluorochrome-conjugated antibody staining and flow cytometry analysis (FCA); and 5) Proliferation and activation of macrophages by intracellular staining and FCA.
RESULTS: Sustained depletion of club cells in CC-DTA mice resulted in weight loss, increased pulmonary cell apoptosis, histopathologic evidence of chronic inflammation, and peribronchiolar lung fibrosis (relative to controls). Lung injury and fibrosis were associated with increased numbers of alveolar macrophages (AMs), monocyte-derived exudate macrophages, and CD8 T cells. We also observed enhanced AM proliferation at day 5 and evidence of increased alternative macrophage activation at day 20.
CONCLUSIONS: Continuous depletion of airway club cells in mice successfully models DR-CB as evidenced by the development of persistent inflammation and chronic airway fibrosis. Increased accumulation of resident and recruited macrophages as well as lymphocytes suggests these cells may contribute to airway fibrogenesis. Ongoing efforts to further characterize this model may enhance our understanding of DR-CB pathogenesis and help identify potential biomarkers and treatments for this disorder.
:

Category (Complete): 23. Occupational, Environmental Health -> Adult -> Cellular/Molecular Investigation /Respiratory Cell and Molecular Biology (RCMB)
Presentation Preference (Complete): Either Poster or Oral
Abstract Affirmations (Complete):
Basic Science Core Track: No
Related to Health Equality?: No
Rare Lung Disease Guide: Yes
If Yes, please select the name of the rare lung disease from the list: Constrictive Bronchiolitis
LMIC: No
Funded by : Department of Defense
I agree to the Author Acknowledgement Statement : True
I agree to the Redundancy Statement : True
I agree to the Prior Publication Statement : True
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Parametric Response Mapping Identifies Increased Functional Small Airways Disease in Soldiers with Biopsy Evidence of Chronic Bronchiolitis

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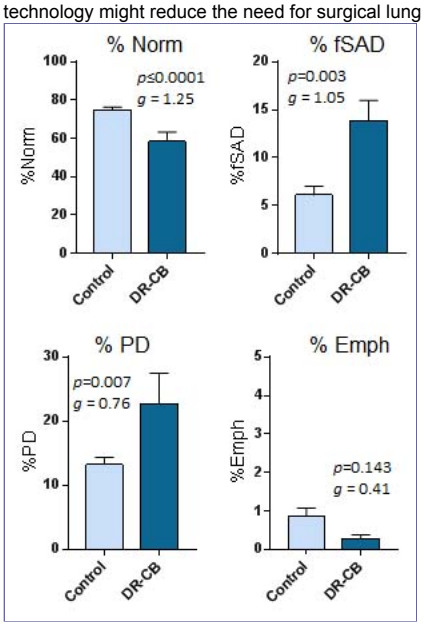
Abstract:
RATIONALE: A subset of soldiers deployed to southwest Asia develop deployment-related chronic bronchiolitis (DR-CB) characterized by persistent small airway inflammation and fibrosis. Inhalational insults are suspected, yet the inciting agents and resultant pathophysiology remains uncertain. Definitive diagnosis of DR-CB requires surgical lung biopsy and no treatments have been identified. Parametric response mapping (PRM) is a computational CT analytic technique that measures differences in lung density on a voxel by voxel basis using paired inspiratory and expiratory high resolution CT scans (HRCTs). Dynamic differences in density characterize each voxel as representing: a) normal lung, b) functional small airways disease (fSAD), c) parenchymal disease, or d) emphysema. The objective of this study was to compare the PRM signatures of HRCTs obtained from a preliminary cohort of soldiers with DR-CB relative to healthy controls.
METHODS. Pre-existing HRCTs were obtained from 18 soldiers diagnosed with constrictive bronchiolitis (≥20% increase in airway wall thickness) following their evaluation at Vanderbilt University Medical Center (detailed in King et al; NEJM 2011). In our current study, the broader diagnostic term “chronic bronchiolitis” is used to acknowledge additional findings of chronic inflammation present in these biopsy specimens. Each HRCT underwent PRM using an established methodology to quantify the percent of lung identified as: a) normal (PRM^{Norm}); b) functional small airways disease (PRM^{fSAD}); c) parenchymal disease (PRM^{PD}); or d) emphysema (PRM^{Emph}). The PRM signatures identified in this cohort was compared with scans obtained from a control cohort of healthy individuals that was matched for sex, age, and smoking status (but not military deployment).
RESULTS: Our analysis demonstrates that $\%PRM^{Norm}$ was significantly decreased in subjects with DR-CB relative to controls (58.56 ± 4.75 DR-CB vs. 74.95 ± 1.35 Cntl; % mean ± SE). Notably, our results identify a 2-fold increase in $\%PRM^{fSAD}$ (13.83 ± 2.13 vs. 6.01 ± 0.93) and a 1.5-fold increase in $\%PRM^{PD}$ (22.66 ± 4.82 vs. 13.25 ± 1.02) whereas the PRM^{Emph} was low and similar between groups (1.22 ± 0.34 vs. 0.28 ± 0.09).
CONCLUSIONS: Our data provides evidence of abnormal PRM signatures on HRCTs obtained from soldiers with biopsy evidence of DR-CB. These preliminary findings raise the exciting possibility that increased fSAD may represent a radiographic biomarker of DR-CB. If supported by subsequent analysis, application of PRM technology might reduce the need for surgical lung biopsies and provide informative when monitoring the natural history of DR-CB or response to treatment.



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Related to Health Equality?: No

Rare Lung Disease Guide: Yes
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