AWARD NUMBER: W81XWH-16-1-0288

TITLE: A Novel Pleiotropic Anti-Inflammatory Drug to Reduce ARDS Incidence

PRINCIPAL INVESTIGATOR: Gary Nieman

CONTRACTING ORGANIZATION: State University of New York, Upstate Medical University
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Upstate Medical University
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

In year one our trauma/hemorrhagic shock (T/HS) injury model was highly effective at causing acute respiratory distress syndrome (ARDS) in all Control groups. However, TRB-N0224 treatment, although it lowered both plasma and bronchoalveolar lavage (BALF) IL-6 levels, resulted in no significant improvement in clinical outcome, which was assessed by lung function (i.e lung compliance or PaO_2/FiO_2 ratio) or histopathology. We postulated that there were two problems with the study: 1) the stress of the gavage was an additional trauma in an already severe T/HS model and 2) the T/HS model causes severe damage to the gut, which significantly reduced TRB-N0224 adsorption. To solve these problems we requested a one-year no-cost extension to use an intravenous formulation of TRB-N0224 that, if our postulate was correct, would solve both of our problems. The results from these experiments were encouraging but not dramatic. The IP formulation of TRB-N0224 significantly reduced the Active and Total MMP-9 in the Bronchoalveolar Fluid (BALF) and Plasma and Interleukin-6 in the BALF and plasma, which translated into a reduction in lung histopathology. Although these are very positive results all of the rats in the TRB-N0224 treatment group died before the end of the 4-hr study period. It is possible that our T/HS model was too severe and that if we reduced the length of HS the positive molecular signal would result in reduced mortality.

15. SUBJECT TERMS

None listed

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	18	**19b. TELEPHONE NUMBER** *(include area code)*

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1. INTRODUCTION:

The goal of this study was to determine the proof of concept that the pleiotropic anti-inflammatory drug, TRB-N0224, was effective at reducing the development of the acute respiratory distress syndrome (ARDS) in a rat trauma/hemorrhagic shock (T/HS) model

2. KEYWORDS:

Acute respiratory distress syndrome, ARDS, systemic inflammatory response syndrome, SIRS, matrix metalloproteinases, MMP, curcumin, TRB-N0224, cytokines

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?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

What *were the major goals of the project*: The goal of this study was to determine the proof of concept that the pleiotropic anti-inflammatory drug, TRB-N0224, was effective at reducing the development of the acute respiratory distress syndrome (ARDS) in a rat trauma/hemorrhagic shock (T/HS) model.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

What was accomplished under these goals: In the first year the IACUC approval was obtained (month 2) and TRB-N0224 was formulated for use and sent to our lab to begin this study (month 5). We began conducting the experiments in the Control groups to confirm that our T/HS model resulted in multiple organ failure, including acute respiratory distress syndrome (ARDS) (months 6-8). Our data clearly showed that T/HS caused ARDS as measured by the fall in PaO_2/FiO_2 ratio and in lung compliance (Fig 1 A,B). Qualitative lung histopathology confirmed that animals had developed an acute lung injury. We discussed with our co-investigator at Stony Brook (Dr. Lorne Golub) what he postulated to be the optimal treatment regimen. The reason for beginning with what we felt was the optimal treatment strategy, was to ensure that the T/HS model was not moribund such that no treatment would work. Dr Golub suggested a 7-day TRB-N0224 pretreatment regimen of by oral gavage (30mg/kg). Experiments with this treatment strategy were conducted in months 8-11.

Unfortunately, we did not measure a physiologic/clinical treatment effect with our postulated optimal treatment strategy (Fig 1A,B). We then analyzed the plasma and bronchoalveolar lavage fluid (BALF) for the inflammatory cytokine IL-6 and showed that TRB-N0224 resulted in a decrease in IL-6 in both plasma and BALF. An Abstract was published using these data and other data from year 1 (Wilcox K, Searles Q, Satalin J, Baker S, Lee H, Aiash H, Gatto LA, Johnson F, Golub L, **Nieman GF**. Novel chemically modified curcumin decreases lung matrix metalloproteinases in a rat ventilation induced lung injury + trauma/hemorrhagic shock model. *Am J Respir Crit Care Med*, 197:A2971, 2018).

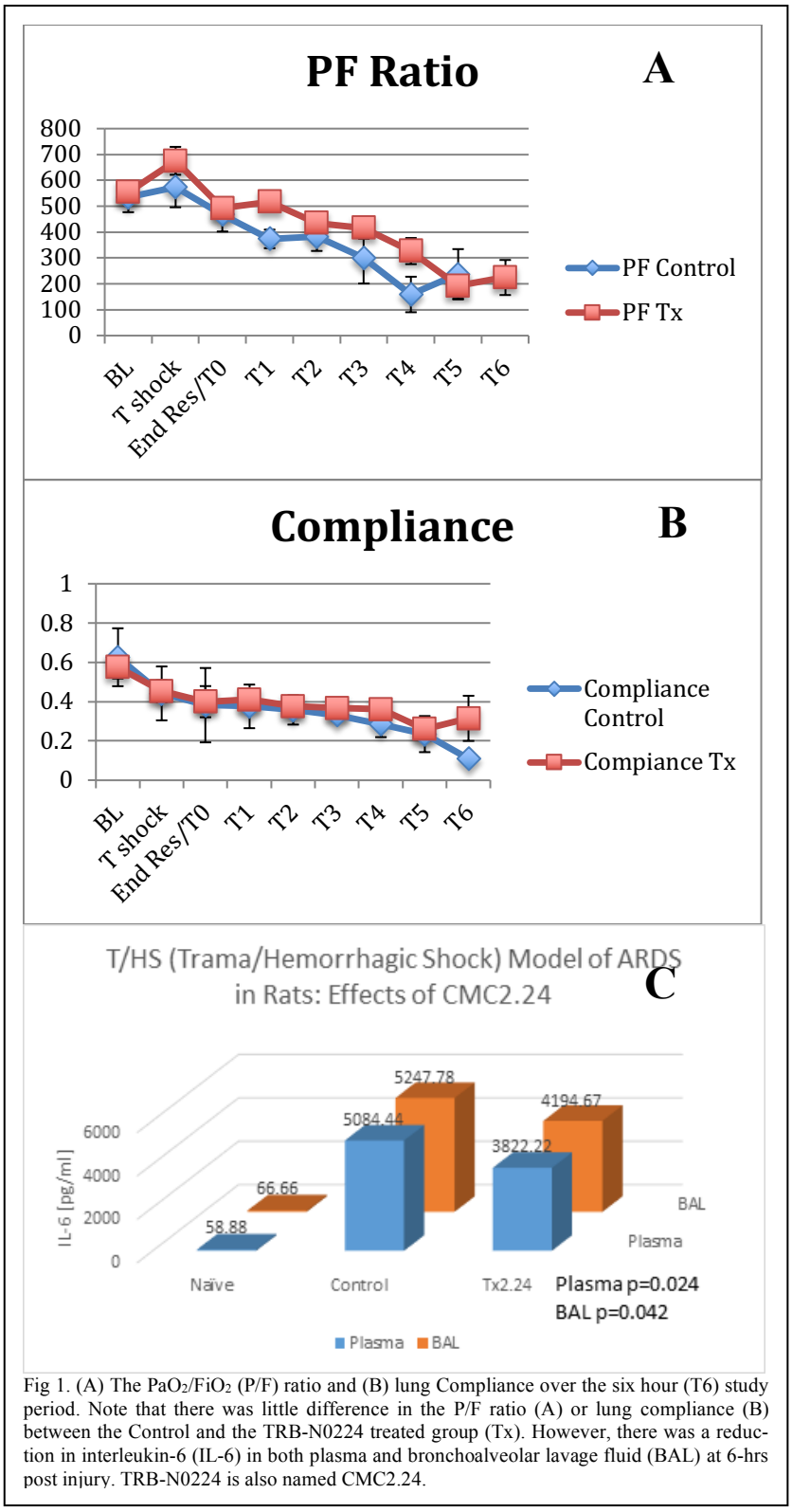

Fig 1. (A) The PaO_2/FiO_2 (P/F) ratio and (B) lung Compliance over the six hour (T6) study period. Note that there was little difference in the P/F ratio (A) or lung compliance (B) between the Control and the TRB-N0224 treated group (Tx). However, there was a reduction in interleukin-6 (IL-6) in both plasma and bronchoalveolar lavage fluid (BAL) at 6-hrs post injury. TRB-N0224 is also named CMC2.24.

We discussed and analyzed the data in month 12 and decided the optimal strategy would be to modify the route of drug delivery from gavage to intraperitoneal (IP). We tested several vehicles and decided to go with an ethanol base vehicle, since TRB-N0224 is not water-soluble. We decided to hold off on the other molecular assays and extensive histopathologic analysis until we have identified the optimal vehicle and dose for TRB-N0224. We requested a 1-year no-cost extension to conduct the IP experiments.

In year 2 the effect of TRB-N0224, was again evaluated in our rat T/HS ARDS model. TRB-N0224 (40mg/kg) was administered I.P. for 3 days prior to lung injury and one final dose was given 30 minutes before surgery. Male Sprague-Dawley rats weighing 375-450g were divided into one of two experimental groups: 1:1 EtOH:Solutol Vehicle or TRB-N0224. Rats were anesthetized with isoflurane and surgically prepared with a tracheostomy and arterial and jugular access. Rats were then mechanically ventilated with the Drager Perseus A500 anesthesia ventilator using a pressure control mode with an inspiratory pressure of 30 cmH_2O, 0 positive end-expiratory pressure (PEEP), 21% inspiratory oxygen fractionation (FiO_2), and a frequency of 45 breaths per minute for one hour.

Rats were bled from their carotid line to maintain a mean arterial pressure (MAP) of 30-35 for 30 minutes. After the 30-minute HS time frame, shed blood was returned along with crystalloid to achieve a MAP of 70. Vitals and arterial blood gases were taken every hour for a maximum of 6 hours. Rats met criteria for euthanasia when they were unable to maintain a MAP above 50 with the aid of crystalloid boluses. At the conclusion of the experiment, the lung was then clamped at inspiration and the lungs were excised and immersed in 10% formalin for histological examination.

Similar to year 1 in which TRB-N0224 given by oral gavage in year 2 with TRB-N0224 given I.P. did not significantly improve clinical lung function measured as a P/F ratio and lung compliance nor did it improve survival (i.e. all TRB-N0224 animals died before the end of the 6hr experiment). TRB-N0224 did, however, significantly reduce the matrix metalloproteinase-9 (MMP-9) activity in the BALF and plasma and reduced the concentration of interleukin-6 (IL-6) in the BALF measured at the end of the experiment (Fig 2). Qualitative lung histology showed that TRB-N0224 reduced the amount of micro-atelectasis, white blood cells in the blood vessels, capil-

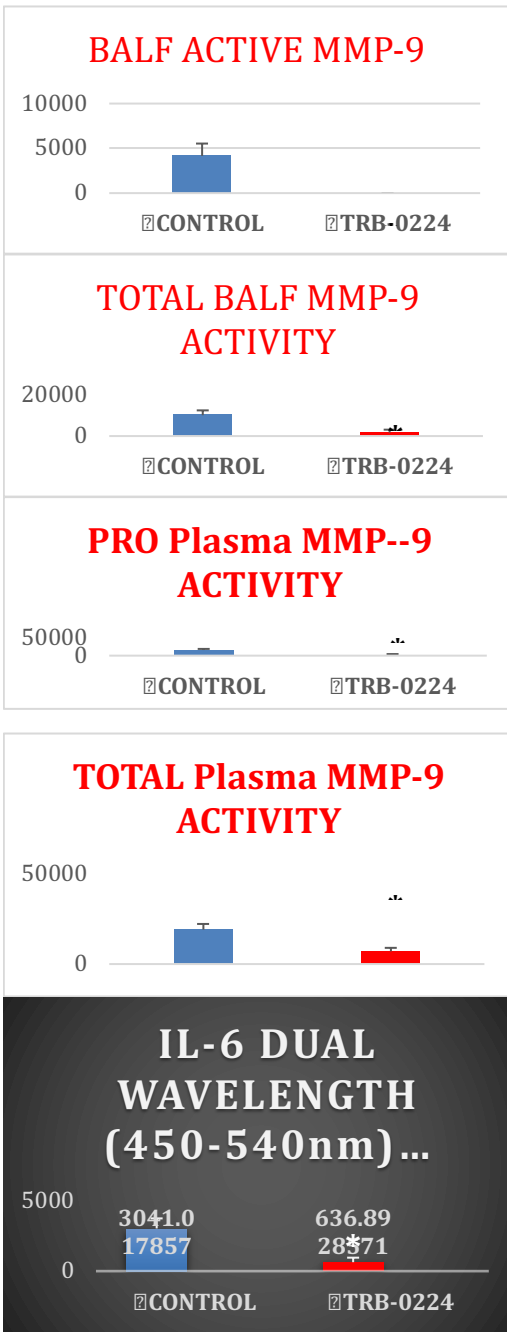

Fig 2. Matrix metalloproteinase-9 (MMP-9) was significantly reduced at the end of the experiment in both the active and pro- form and in the bronchoalveolar lavage fluid (BALF) and plasma in the TRB-N0224 as compared with the Control group. Interleukin-6 (IL-6) was also decreased in the TRB-N0224 group BALF as compared with the Control group.

lary congestion, and cellular infiltration and alveolar flooding with edema as compared with the Control group. There were little differences between the Control and TRB-N0224 groups in the liver, intestine, spleen or kidney histopathology. We will write and submit an abstract on the year 2 data.

Conclusions: In our severe T/HS rat ARDS model TRB-N0224 had a positive molecular impact in the BALF and in the plasma. Lung histopathology was also reduced by IP TRB-N0224 administration. However, no clinical difference was seen between groups. These results suggest that TRB-N0224 should be tested in a less severe T/HS ARDS model or animal models of sepsis-induced ARDS to see if the positive anti-inflammatory effect will translate into a positive clinical effect.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

The surgical resident training in my lab, Dr. Kailyn Wilcox, helped to conduct these experiments and she wrote and presented a paper using the year 1 data:

Wilcox K, Searles Q, Satalin J, Baker S, Lee H, Aiash H, Gatto LA, Johnson F, Golub L, Nieman GF. Novel chemically modified curcumin decreases lung matrix metalloproteinases in a rat ventilation induced lung injury + trauma/hemorrhagic shock model. *Am J Respir Crit Care Med*, 197:A2971, 2018

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

An abstract was presented at the American Thoracic Society Congress on the year 1 data (see below) and we will also construct and submit an abstract on the year 2 data.

Wilcox K, Searles Q, Satalin J, Baker S, Lee H, Aiash H, Gatto LA, Johnson F, Golub L, Nieman GF. Novel chemically modified curcumin decreases lung matrix metalloproteinases in a rat ventilation induced lung injury + trauma/hemorrhagic shock model. *Am J Respir Crit Care Med*, 197:A2971, 2018

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to Report

4. **IMPACT:** D*escribe 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Our results were inconclusive in the sense that we had a positive impact on the inflammatory mediators but no impact on the clinical outcome. It is possible that the injury model was too severe and the animals where moribund and that we would also see a positive clinical impact in a different animal model. Since we did find a positive anti-inflammatory impact of the drug we believe that further testing is necessary to determine the potential of this drug as a treatment for the acute respiratory distress syndrome (ARDS). We also feel it important that an IV formulation of drug be developed before further testing as a drug to prevent the development of ARDS

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

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:*

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

The experiments in year 1 went as planned but the inclusive results lead us to request the 1-year extension to test a second route of drug administration. These experiments also went as expected with similar results except that we did see a positive treatment effect of TRB-N0224 on lung histopathology with the IP route of drug administration as compared with the oral gavage route.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

There was no impact on expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals

No changes were made in our IACUC except for the route of drug delivery from oral gavage to IP.

Significant changes in use of biohazards and/or select agents

There were no changes in the biohazards of the agent (TRB-N0224) used.

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. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or*

series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Wilcox K, Searles Q, Satalin J, Baker S, Lee H, Aiash H, Gatto LA, Johnson F, Golub L, Nieman GF. Novel chemically modified curcumin decreases lung matrix metalloproteinases in a rat ventilation induced lung injury + trauma/hemorrhagic shock model. *Am J Respir Crit Care Med*, 197:A2971, 2018

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	*Gary Nieman*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.8 Calendar Months*
Contribution to Project:	*Mr. Nieman will be responsible for directing the research that will take place at SUNY Upstate Medical Center. Along with his co-investigators, will make any necessary adjustments to the experimental model, as well as, analyze, interpret and construct manuscripts that result from the data.*
Funding Support:	*NIH/NHLBI R01HL131143*
Name:	*Joshua Satalin*
Project Role:	*Research Scientist*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0002-7582-2493*
Nearest person month worked:	*6.0 Calendar Months*
Contribution to Project:	*Mr. Satalin* He will supervise all personnel and oversee all operations of the laboratory. In addition to the managerial duties, Mr. Satalin will be intimately involved in every aspect of the research proposed, including but not limited to; assisting in animal surgery, training a new technician, conducting experiments, manuscript editing and preparation.
Funding Support:	*NIH/NHLBI R01HL131143*

Name:	*Hani Aiash*
Project Role:	*Research Scientist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6.0 Calendar Months*
Contribution to Project:	*Dr. Aiash was played an integral role in the hemorrhage model. His 20+ years of clinical experience helped guide many of the decisions relating to the well-being of the animal as well as how to respond to changes in hemodynamics.*
Funding Support:	W81XWH-16-1-0288

Name:	*Louis Gatto*
Project Role:	*Adjunct Professor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.2 Calendar Months*
Contribution to Project:	*Dr. Gatto was instrumental in developing a method to analyze both alveolar and alveolar duct micro-strain using a histologic technique. These techniques are essential to testing of the hypothesis of our proposal and will be under the direct supervision of Dr. Gatto. His input will be extremely valuable in helping the PI and co-investigators, in making any necessary adjustments to the experimental model, as well as, analyze, interpret and construct manuscripts that result from the data.*
	Paid a salary as a faculty member at Cortland College
Name:	*Kailyn Wilcox*
Project Role:	*Surgical Resident*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*5*
	Dr. Wilcox was responsible for the surgical preparation of the animals, conducting the experiments, collecting and analyze the data.
Funding Support:	*Paid as a Surgical Resident by New York State.*

Name:	*Lorne Golub*
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*0.24 Calendar Months*
Contribution to Project:	Together with the PI, Dr. Golub will make necessary ad justments to the experimental model, analyze, interpret and write up the data for publication. He will provide technical oversight for the biochemical analyses to be performed by Stony Brook University.
Funding Support:	*Paid as a Faculty at SUNY Stony Brook.*

Name:	*His-Ming Lee*
Project Role:	*Assistant Professor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3.6 Calendar Months*
	Dr. Lee will perform the all biochemical analyses of MMP and elastase activity, as well as cytokine levels and drug concentrations.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

SUNY Stony Brook, Stony Brook NY. The group at Stony Brook lead by Dr Lorne Golub measured the inflammatory mediators in the bronchoalveolar lavage fluid (BALF) and plasma.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *N/A*
QUAD CHARTS: *N/A*

9. APPENDICES: *NA/*