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TITLE: Modulating MAVS Aggregation to Promote Host Resilience During Bacterial Pneumonia

PRINCIPAL INVESTIGATOR: Min-Jong Kang, MD, PhD

RECIPIENT: Yale University, New Haven, CT

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5d. PROJECT NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our proposal is focused on the Mitochondria Antiviral Signaling (MAVS) pathway, as a key contributor to the impaired host tolerance by causing pathological inflammatory and injury response during bacterial lung infections. The goal of our study is to gain in depth understanding of MAVS regulatory mechanisms during bacterial infection and find optimal therapeutic options that limit MAVS and promote host tolerance or resilience during pulmonary bacterial infections. We hypothesize that MAVS aggregation contributes to uncontrolled inflammatory and cell death responses leading to exacerbated tissue injury. Our aims are the following: to characterize MAVS aggregation, its disaggregation and impact on host pathological response during bacterial lung infection, To investigate mechanisms that limit MAVS-mediated dysregulation of host resilience to limit pathologic consequences of Pseudomonas infection, and to determine the clinical and biological relevance of the MAVS aggregation and its regulation by PINK1 in patients with bacterial pneumonia. The ultimate goal is to develop new and viable therapeutic strategies to regulate MAVS response during the bacterial infection to help the host better deal with the infections by limiting pathological inflammation without compromising the bacterial clearance.

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			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*

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

Bacterial pneumonia represents substantial challenges in medicine and health care system. Using the mouse modeling system and human samples from patients, we have identified important immune pathways that may disrupt host resilience and contribute to increased pathology in bacterial pneumonia. We will investigate how mitochondrial innate immune signaling pathways play uncontrolled inflammatory and cell death responses leading to exacerbated tissue injury without affecting bacterial clearance. **The overall goal of the studies is to characterize how the MAVS and PINK1 molecules, crucial regulators of mitochondrial innate immunity, impact on the host -pathological response during bacterial lung infection and define its underlying mechanisms. Further, we will determine the clinical and biological relevance of the MAVS activation and its regulation by PINK1 in patients with bacterial pneumonia.**

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

Lungs, pneumonia, infections, Pseudomonas, MAVS (Mitochondrial Anti-viral Signaling), PINK1, innate immunity, inflammation, cell death, host resilience, sepsis

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.

Major Goals/Milestones:
Specific Aim 1:

1. Major Task 1: Subtask 1: Yale IACUC Approval & ACURO Approval: 100% completed
2. Major Task 1: Subtask 2: Mouse model of Pseudomonas lung infection: 30% completed
3. Major Task 1: Subtask 3: Evaluation of MAVS aggregation kinetics and resolution: 30%
4. Major Task 1: Subtask 4-5: Analyses of MAVS associated signaling & proteins: 25%
5. Major Task 2: Subtask 1-3: Evaluate role of MAVS in host resistance and host resilience: 25% completed
6. Major Task 3: Subtask 1-4: Pathogen factors in MAVS aggregation: 0% completed

Specific Aim 2

7. Major Task 1: Subtask 1-4: Role of PINK1 in regulating MAVS aggregation and disaggregation during bacterial infection: 20% completed
8. Major Task 2: Subtask 1-3: Role of PINK1 in regulating cell death, tissue injury and host resilience in mice: 0% completed
9. Major Task 3: Subtask 1-2: Use of neo-substrate & ABT-263: 20% completed
10. Major Task 3: Subtask 3: Immunological, bacterial and pathological measures: 0% completed

Specific Aim 3

11. Major Task 1: Subtask 1-6: Characterization of MAVS and PINK1 in patients: 0% completed
12. Major Task 2: Subtask 1-4: Activation of MAVS aggregation and regulation by PINK1 in human samples: 0% completed
13. Major Task 3: Subtask 1-3: Perform ex vivo precision cut human lung slices (PCLS) to study MAVS during bacterial infection: 0% completed

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.

This reporting period represents our research progress conducted within the first year of receiving grant funding. As a crucial initial step to test our overarching hypothesis, we evaluated the alteration status of multimeric MAVS aggregation and its related biological significances in the setting of murine modeling of *Pseudomonas aeruginosa* pneumonia (Figure 1).

For lung infection in C57BL/6 mice, live *pseudomonas aeruginosa* (PA) was injected using intratracheal instillation surgery. Then, Hematoxylin and Eosin (H&E) staining was performed to confirm pseudomonas aeruginosa (PA)-induced lung infiltration (Figure 1a). When Semi-Denaturating Detergent Agarose Gel Electrophoresis (SDD-AGE), an established method to evaluate the multimeric formation of a molecule, was performed to confirm MAVS aggregation in whole lung lysates, the result revealed that MAVS aggregation was significantly observed 16 hours after the PA infection (Figure 1b). Next, sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) was performed to evaluate the expression of NLRP3, an essential component of inflammasomes – a central player of innate immunity - in whole lung lysates. Indeed, NLRP3 expressions were increased 16 hours after the PA infection (Figure 1b). In line with the above findings, cell-free double-strand DNA (cf-dsDNA) and interleukin-1 beta (IL-1β) were increased 16 hours after the PA infection (Figure 1c). Collectively, these findings suggest an activation of the immune response to the infection and imply that MAVS has a correlation with the host's defense against pseudomonas aeruginosa in the lungs. **These results are related to the topic "Mouse model of Pseudomonas lung infection" (Major Task 1 of Specific Aim 1) and "Evaluation of MAVS aggregation kinetics and resolution" (Major Task 1 of Specific Aim 1).**

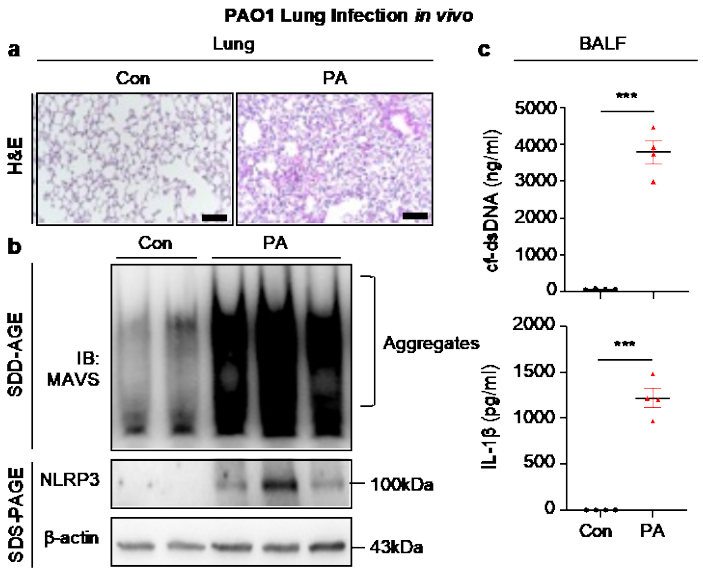

Figure 1. MAVS aggregation was observed in pseudomonas aeruginosa infected mice lung. For lung infection in C57BL/6 mice live pseudomonas aeruginosa (PA) was injected using intratracheal instillation surgery. **a.** Hematoxylin and Eosin (H&E) staining was performed to confirm pseudomonas aeruginosa (PA)-induced lung infiltration. Lung infiltration can be observed in conditions like pneumonia, where the immune system responds to an invading pathogen. **b.** SDD-AGE was performed to confirm MAVS aggregation in whole lung lysates, and as a result, MAVS aggregation was observed 16 hours after the PA infection. SDS-PAGE was performed to confirm NLRP3 expressions in whole lung lysates, and as a result, NLRP3 expressions were increased 16 hours after the PA infection. β-actin was used as the loading control. **c.** To estimate damage-associated molecular pattern (DAMP) and inflammation in bronchoalveolar lavage fluid (BALF), we investigated cell-free double-strand DNA (cf-dsDNA) and interleukin-1 beta (IL-1β) using PicoGreen dsDNA Assay kit and ELISA respectively, and as a result, cf-dsDNA and IL-1β were increased 16 hours after the PA infection. These findings suggest an active immune response to the infection and imply MAVS has a correlation with the host's defense against pseudomonas aeruginosa in the lungs.

To determine the role of MAVS in modulating host resilience in bacterial infection, we employed an *in vivo* murine modeling of sepsis. As revealed in the definition of sepsis, which is defined as life-threatening organ

dysfunction caused by a dysregulated host response to infection, the sepsis study provides valuable information in investigating the role and the mechanisms underlying host resilience during infection.

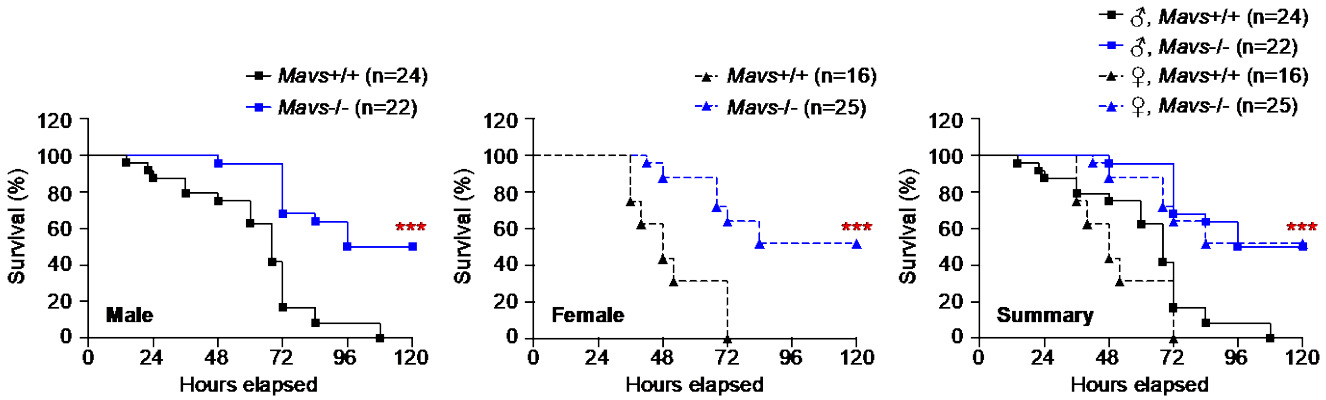

Figure 2. MAVS deficiency elevated the survival rate in the LPS-induced sepsis model. To induce sepsis in wild-type (*Mavs+/+*) or MAVS (*Mavs-/-*) knockout C57BL/6 mice, 5 mg/kg LPS was injected intraperitoneal (*i.p.*) and then primed for 4 hours. Afterward, for the challenge, 10mg/kg LPS was injected *i.p.* The experiment was performed on both males and females, and the number of animals was as follows; male *MAVS*+/+: 24, male *MAVS*-/-: 22, female *MAVS*+/+: 16, female *MAVS*-/-: 25. As a result of the experiment, the survival rate significantly increased when both males and females were deficient in MAVS. These findings indicate that MAVS deficiency had a protective effect against the mortality associated with sepsis in this experimental model. MAVS is typically involved in the host's response to viral infections, but its deficiency appears to be beneficial in the context of this bacterial endotoxin-induced sepsis model.

Specifically, we induced sepsis *in vivo* in wild-type (Mavs+/+) or MAVS (Mavs-/-) knockout C57BL/6 mice following an established protocol (please refer to Figure 1 legend for more detailed information). Intriguingly, the mice in which MAVS is genetically null mutated showed remarkable survival benefits in our modeling of sepsis *in vivo* (Figure 1). The survival benefits were observed in a similar pattern from both male and female mice. These findings indicate that MAVS activation and its distal signaling may constitute a crucial force to disrupt host resilience in infectious disorder. **These results are related to the topic "Evaluate role of MAVS in host resistance and host resilience" (Major Task 2 of Specific Aim 1).**

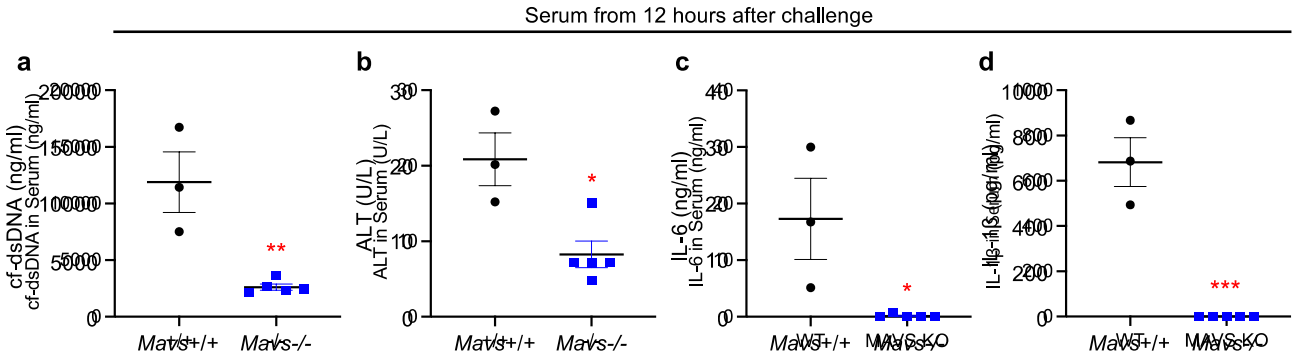

Figure 3. MAVS deficiency decreased damage-associated molecules and inflammation in the LPS-induced sepsis model. The serums were isolated from blood samples collected 12 hours after the challenge. **a and b.** To estimate damage-associated molecules in serums, we investigated cell-free double-strand DNA (cf-dsDNA) and alanine aminotransferase (ALT) using PicoGreen dsDNA assay kit and ALT activity assay kit respectively, and as a result, cf-dsDNA and ALT were decreased both when deficient in MAVS. **c and d.** To estimate inflammation in serums, we investigated interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) using ELISA assay, and as a result, IL-6 and IL-1β were decreased both when deficient in MAVS. Overall, the experiment's results suggest that MAVS deficiency had a protective effect in the LPS-induced sepsis model. MAVS deficiency was associated with decreased levels of damage-associated molecules (cf-dsDNA and ALT) and reduced inflammation (IL-6 and IL-1β) in the serum.

Next, we initiated evaluations aimed at pinpointing molecular alterations that would serve as a roadmap for exploring the role of MAVS that disrupts host resilience in our modeling (refer to Figure 3). After thorough consideration, we examined molecular changes in serum samples from our in vivo model at the 12-hour time point following the LPS challenge, which is at the 16-hour time point from the LPS priming in our sepsis model. This specific time point corresponds to a later phase in the progression of sepsis, where the observed findings likely shed light on MAVS' functional impact on host resilience long after the acute pathogen-driven inflammatory phase is subsided. Interestingly, at this time point, cell-free double-strand DNA (cf-dsDNA) (Figure 3a) and alanine aminotransferase (ALT) (Figure 3b) were significantly regulated via a MAVS-dependent manner. In addition, interleukin-6 (IL-6) (Figure 3c) and interleukin-1 beta (IL-1β) (Figure 3d) in serums were also remarkably decreased in MAVS deficiency *in vivo*. Overall, the experiment's results further confirm that MAVS is a critical driving force to disrupt host resilience. In addition, the results provide important clues to investigate the underlying mechanisms by which MAVS undermines host resilience. **These results are related to the topic "Analyses of MAVS associated signaling & proteins" (Major Task 1 of Specific Aim 1).**

What opportunities for training and professional development have 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 studies have resulted in several training opportunities by 1) promoting proficiency in evaluating in the lung compartment in the mouse infection samples; 2) proficiency in *in vitro* culture systems; 3) proficiency in mouse handling; and 4) proficiency in lung physiologic, cellular, and molecular assays.
Professional development activities include broadening of scientific knowledge in lung biology, evaluations of MAVS pathways and the presentation of the results at Yale Pulmonary meetings and national conferences.

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.

Preliminary results were disseminated through open presentations and discussion with other investigators.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

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

The next set of goals and milestones to achieve are the following:

1. Evaluation of MAVS aggregation and processing.
2. Evaluation of the regulatory mechanisms underlying MAVS aggregation/activation
3. Evaluations of pathogen factors involved in MAVS aggregation
4. Evaluation of MAVS and PINK1 interactions.
5. Evaluation of PINK1-mediated inhibitory mechanisms of MAVS aggregation/activation
6. Evaluation on intervention studies to modulate MAVS aggregation in bacterial infection studies.
7. Procurement of human samples bacterial respiratory infection samples, previously collected as well as through new recruitment.

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?
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 initial studies have revealed a noteworthy aggregation of MAVS during bacterial pneumonia in a mouse model, representing a previously unprecedented and novel discovery. In this context, reduced MAVS activity in the mouse led to a diminished inflammatory response, including reduced inflammasome activation. These findings extend to other bacterial infections, such as MRSA. Our results from *in vivo* murine sepsis modeling highlight the crucial role of MAVS-mediated signaling in disrupting host resilience and tolerance

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.

Our studies will have a significant impact on the field of pneumonia by enhancing our understanding of the interplay between respiratory infections in the lungs and the host's immune-modulating responses mediated by MAVS. This research represents a substantial conceptual leap, shedding light on the pivotal role of MAVS signaling. While MAVS is traditionally recognized for its importance in antiviral immunity, our findings suggest it can also be a critical factor in undermining host resilience during bacterial pneumonia. This work could identify therapeutic options to modulate exuberant inflammation in response to bacterial infections. This work could potentially identify similar mechanisms by which MAVS modulate other organ infections and inflammatory processes.

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.*

Not applicable

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.*

If our studies reveal that MAVS plays a central role in orchestrating excessive and detrimental inflammation during bacterial infections, this breakthrough could open the door to significant therapeutic and diagnostic advancements. The identification of MAVS as a key regulator may pave the way for the development of MAVS inhibitors or antagonists, which could potentially be used as therapeutic agents to modulate the immune response and mitigate the harmful effects of inflammation in bacterial lung infections. Moreover, the recognition of MAVS as a diagnostic marker may enable us to identify at-risk patients who are more likely to develop severe acute lung injury during bacterial lung infections. By pinpointing these patients early on, we can tailor more precise and proactive medical interventions to enhance their outcomes and overall patient care.

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
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

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.

Currently no delays. We do not anticipate any issues of conducting the proposed work at Yale. As the partnering PI of the current proposal, our laboratory is mainly dedicated to conduct murine studies and *in vitro* works as well. A notable change has occurred recently, though. Dr. Dela Cruz is moving to UPMC in Pittsburgh and working on transfer of his DOD grant. Transferring process of MAVS KO and PINK1KO mice are underway. Dr Dela Cruz also has previously collected biorepository human samples that could be used for this study and is working on HRPO approval. UPMC has a robust clinical repository and recruitment of new patients with lung injury and infection which Dr. Dela Cruz will be part of. Our (Dr. Kang's) laboratory will continue extensively a collaboration with Dr. Dela Cruz's research group. The move of Dr. Dela Cruz group will not impact completion of the studies; We will have Zoom meeting as the monthly basis, and will visit each other's lab meetings frequently for a continuing collaboration.

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 were no significant changes that impacted 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

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

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).*

We are currently completing 2 manuscripts reporting our findings.

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.*

- 2023 Yale Pulmonary, Critical Care, and Sleep Medicine (PCCSM) Research Seminar Series: *"NLRX1: Bridging Aging Biology and Lung Disorders as the Sole Mitochondrial Molecule in NLR Family"*
- 2023, GENENTECH Research Seminar Series: "*COPD Drug Discovery Strategy: Targeting a common mechanistic denominator underlying COPD heterogeneity*"
- 2022, NIH/NHLBI Workshop, Mitochondria in the pathogenesis of lung and sleep disorders: "*Mitochondrial Anti-viral Signaling (MAVS) in IPF Pathobiology: Intricate connections of mitochondrial dysfunction, inflammasome, and cellular senescence*"
- 2022, Korea, Seoul National University Hospital, Macrophage Biology Seminars: "*Mitochondrial Regulation of Innate Immune Signaling in Health & Disease*"
- 2022, 26th Asian Pacific Society of Respiratory Congress (APSR) : Cell & Molecular Biology – New Potential Therapeutics in Respiratory Diseases / "*Mitochondrial regulation of innate immune signaling & pulmonary diseases*"

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".

Name:	*Min-Jong Kang, MD, MPH, PhD*
Project Role:	*Principal Investigator (Partnering PI with Dr. Dela Cruz)*
Researcher Identifier (e.g. ORCID ID):	*n/a*
Nearest person month worked:	*3.6*
Contribution to Project:	*Dr. Kang supervised the overall design, experimental planning and data interpretation for all the studies.*
Funding Support:	*CDMRP* PR211819P1

Name:	*Hyeon Jun Shin, PhD*
Project Role:	*Co-Investigator*

Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: *6*
Contribution to Project: *Dr. Shin has performed murine studies and evaluated the results..*
Funding Support: *CDMRP* PR211819P1

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.*

Nothing to Report

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.

Not applicable

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

Not applicable

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.

None