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TITLE: Therapeutic Benefit of Hsp90 Inhibition in Pulmonary Fibrosis

PRINCIPAL INVESTIGATOR: Satish K Madala

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Cincinnati, OH 45229

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

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Children's Hospital Medical Center

Cincinnati, OH 45229

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14. ABSTRACT

IPF is a fatal fibrotic lung disease associated with aberrant activation of fibroblasts and progressive fibrosis. The pirfenidone therapy for IPF has been shown to slow the rate of decline in lung function but do not halt ongoing fibrosis. This application will test whether inhibition of HSP90 activity, coupled with anti-fibrotic therapy of pirfenidone, will attenuate WT1-driven fibroblast activation. The proposed studies will provide robust, highly novel observations to rapidly pursue the long-term goal: Translational exploration of the molecular mechanisms by which HSP90 activity positively regulates IPF pathogenesis in order to devise novel preventive and therapeutic strategies for IPF

15. SUBJECT TERMS-

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**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.*

IPF is a fatal fibrotic lung disease associated with aberrant activation of fibroblasts and progressive fibrosis. The pirfenidone therapy for IPF has been shown to slow the rate of decline in lung function but do not halt ongoing fibrosis. This application will test whether inhibition of HSP90 activity, coupled with anti-fibrotic therapy of pirfenidone, will attenuate WT1-driven fibroblast activation. The proposed studies will provide robust, highly novel observations to rapidly pursue the *long-term* goal: Translational exploration of the molecular mechanisms by which HSP90 activity positively regulates IPF pathogenesis in order to devise novel preventive and therapeutic strategies for IPF.

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

Idiopathic Pulmonary fibrosis; Fibroblasts; Heat shock protein 90; Wilms' tumor 1; lung; collagens

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.

Specific Aim 1: To determine the role of HSP90 in fibroblast activation in IPF
The major task is to determine which HSP90 isoform is involved in fibroblast activation.

Subtask 1: Obtain regulatory approvals: ACURO and HRPO review (Duration: 3-6 months)
Subtask 2: Develop lentiviral plasmids to overexpress HSP90AA or HSP90AB isoforms to assess changes in fibroblasts activation. (Duration: 1-12 months)
Subtask 3: Develop lentiviral plasmids to knockdown HSP90AA or HSP90AB isoforms to assess changes in fibroblast activation (Duration: 7-24 months)
Subtask 4: Develop lentiviral plasmids to overexpress wild type and D88N-HSP90 (a dominant negative mutant of HSP90) to assess changes in fibroblast activation (Duration: 12-24 months)

Specific Aim 2: Define the physiological and functional relevance of HSP90-WT1 interaction in fibroblast activation
The major task is to identify contributions of HSP90 and WT1 on fibroblast activation.

Subtask 1: Knockdown HSP90AB, WT1 or both to assess changes in fibroblast-specific gene networks and function. (Duration: 1-24 months)
Subtask 2: Overexpress HSP90AB, WT1 or both to assess changes in fibroblast-specific gene networks and function (Duration: 12-24 months)
Subtask 3: Overexpress D88N-HSP90 and WT1 alone or together to assess changes in fibroblast-specific gene networks and function (Duration: 12-36 months)

Specific Aim 3: Determine whether combined therapy using pirfenidone and 17-AAG is effective to reverse established and ongoing pulmonary fibrosis

The major task is to determine if combined therapy of 17-AAG and Pirfenidone attenuates fibrosis in vivo.

Subtask 1: Utilize a mouse model of TGFα-induced pulmonary fibrosis to test if combined therapy of 17-AAG and Pirfenidone attenuates fibrosis (Duration: 6-24 months)

Subtask 2: Utilize a mouse model of bleomycin-induced pulmonary fibrosis to test if combined therapy of 17-AAG and Pirfenidone attenuates fibrosis (Duration: 16-36 months)

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.

1. **Major activities:** The first 8-10 months of funding for this project have been focused upon several key start up areas, including i) protocol and manual operation development, ii) obtaining all regulatory approvals including ACURO and HRPO (100% Completed), and iii) initiated studies to breed up mice and develop lentiviral plasmids to overexpress or knockdown WT1, D88N-HSP90, HSP90AA, HSP90AB isoforms to assess changes in fibroblasts activation. (50-60% completed).
2. **Specific objectives:** The objectives of this are captured in the specific aims described above, but can be succinctly summarized in three aims: Aim 1) To determine the role of HSP90 in fibroblast activation in IPF; Aim 2) Define the physiological and functional relevance of HSP90-WT1 interaction in fibroblast activation, and Aim 3) Determine whether combined therapy using pirfenidone and 17-AAG is effective to reverse established and ongoing pulmonary fibrosis.
3. **Significant results:**

   Aim 1: Subtask 1: Obtain regulatory approvals: ACURO and HRPO review (Duration: 3-6 months): Completed with couple of rebuttals in 2018.

   Subtask 2: Develop lentiviral plasmids to overexpress HSP90AA or HSP90AB isoforms to assess changes in fibroblasts activation. (Duration: 1-12 months). Our published data demonstrated reduced HSP90AB but not HSP90AA attenuates proliferation and ECM production in fibroblasts isolated from fibrotic lesions of TGFα mice (***JCI Insight 2017***). In this subaim, we will use normal fibroblasts and IPF fibroblasts for HSP90AA or HSP90AB overexpression. In the first year, our work on using primary cells is still under progress and hope to achieve set goals in the next year as we completed obtaining ACURO and HRPO approvals. We recently completed cloning of dominant negative isoform of HSP90AB (D88N-HSP90; **Figs 1 & 2**)) and studies are in progress to generate other (HSP90AA and HSP90AA) clones using site-directed mutagenesis methods.

   Subtask 3: Develop lentiviral plasmids to knockdown HSP90AA or HSP90AB isoforms to assess changes in fibroblast activation (Duration: 7-24 months). We developed the efficient and isoform-specific knockdown method for inhibiting the expression of HSP90AA and HSP90AB isoforms using stealth silencer RNA method (**Fig 3**).

Subtask 4: Develop lentiviral plasmids to overexpress wild type and D88N-HSP90 (a dominant negative mutant of HSP90) to assess changes in fibroblast activation (Duration: 12-24 months): This subaim will determine the effect of wild type and D88N-HSP90 forced expression on activation of IPF fibroblasts, including proliferation, invasion, and apoptosis. Earlier structural studies have demonstrated that Asp93 in HSP90 makes a direct hydrogen bond to the exocyclic N6 group of adenine of bound ATP/ADP nucleotide and site-directed mutagenesis of Asp88 to asparagine (D88N) in HSP90AB resulted in the loss of ATP binding and ATPase activity. We completed the cloning of human-HA-N-Hsp90βDN in pCDNA3 using standard cloning methods (Addgene Plasmid #22480). Clones were confirmed by DNA sequencing. To determine the effect of D88N-HSP90, we transfected HEK293 cells with control and D88N-HSP90 and measured D88N-HSP90 protein expression and effect on migration of HEK293 cells. In support to our hypothesis, we observed a significant increase in the expression of D88N-HSP90 that resulted in decrease in the migration of HEK293 cells compared to control cells (**Fig 1**). To overexpress D88N-HSP90 using lentivirus, we used pLenti vector (pLJM1-EGFP) to clone HA-N-Hsp90βDN (**Fig 2**). Agarose gel analysis of pLento-HA-N-Hsp90βDN digestion with restriction enzymes Nhe1 and EcoR1 confirms the generation of lentiviral clone of D88N-HSP90. Studies are in progress to generate additional clones using the above startegy.

Aim 2: Subtask 1: Knockdown HSP90AB, WT1 or both to assess changes in fibroblast-specific gene networks and function. (Duration: 1-24 months): We obtained regulatory approval for primary cell culture and studies are in progress to knockdown HSP90AB and alone or in combination to determine fibroblast specific gene networks. In particular, we completed the knockdown of WT1 in primary fibroblasts and identified WT1-driven gene networks in fibroblasts. These new findings are now published in JCI Insight 2018.

Subtask 2: Overexpress HSP90AB, WT1 or both to assess changes in fibroblast-specific gene networks and function (Duration: 12-24 months): Work in progress

Subtask 3: Overexpress D88N-HSP90 and WT1 alone or together to assess changes in fibroblast-specific gene networks and function (Duration: 12-36 months): Work in progress

4. **Significant results:** As noted above, we have completed the start-up phase of our studies and the major findings are now published in high-impact journal (JCI insight 2018). We have completed cloning of D88N-HSP90 and validated expression using HEK293 cells (**Fig 1**). Also, we completed the generation of lentiviruses to overexpress human and mouse WT1 (**JCI insight 2018; Figure 3**). The effects of WT1 overexpression on fibroblast activation are now completed and the findings were published in ***JCI insight 2018*** **(Figures 3-4)**. This study also describes the knockdown effects of WT1 on fibroblast activation. Similarly, we evaluated the specific effects of Hsp90AA or Hsp90AB isoforms on fibroblast activation. In particular, our knockdown studies have identified potential differences between Hsp90AA and Hsp90AB isoforms on fibroblast activation. For Aim3, we completed to set-up breeders to generate wild type and TGFα transgenic mice. Initial studies are completed to evaluate the effects of 17-AAG and pirfenidone in the pathogenesis of TGFα-induced pulmonary fibrosis. In support to our hypothesis, pharmacological inhibition of Hsp90 activity or the genetic loss of WT1 has attenuated fibroblast activation and pulmonary fibrosis. Currently, studies are in progress to evaluate whether inhibition of Hsp90 with 17-AAG in a mouse model of bleomycin-induced pulmonary fibrosis will also have similar effects observed with mouse model of TGFα-induced pulmonary fibrosis. Breeding of TGFα mice is in progress to test the effect of combination therapy.

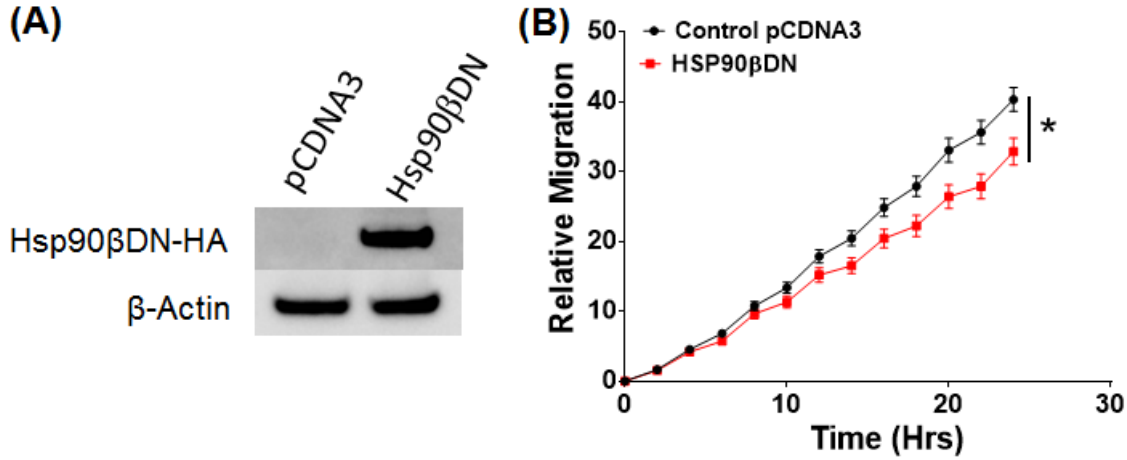

Figure 1. (A) HEK293 cells were transfected with control (pCDNA3) or Hsp90βDN plasmid and cell lysates were immunoblotted with anti-Hsp90 and β-actin antibodies. (B) Scratch wound migration assay was performed on HEK293 cells transfected with control or Hsp90βDN overexpressing plasmid for 24hr. Quantitation of migration represented as relative migration over time. Data shown are mean ± SEM values. Statistical significance between groups was measured using ANOVA. *p<0.05.

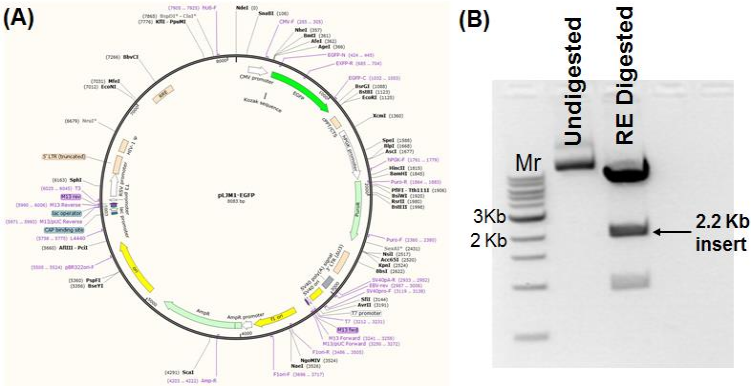

Figure 2. (A) The map of pLJMI-EGFP vector and D88N-HSP90 gene inserted using restriction enzymes, Nhe1 and Age1. (B) Agarose gel showing the right insertion and orientation of D88N-HSP90 in Lenti vector using restriction enzyme digestion (Age1 and EcoR1).

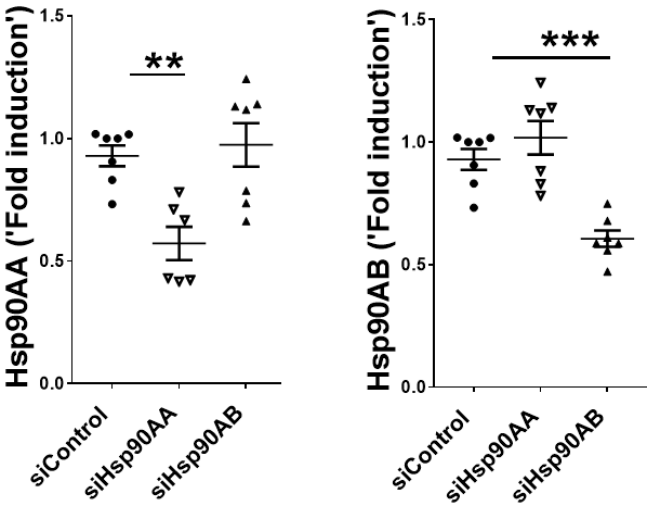

Figure 3: Primary Lung resident fibroblasts were isolated from lung cultures of TGFα mice which was placed on Dox for 4wk using anti-CD45 magnetic beads and transfected with either control or Hsp90 isoform specific siRNA for 72 hr. (A) The transcripts for Hsp90AA and (B) Hsp90AB isoform are shown as the fold induced by normalizing to HPRT control. Data are cumulative of 2 independent experiments with similar results. Data shown are mean + SEM values (n = 7). Statistical significance between groups was measured using an ANOVA. **p<0.005 and ****p<0.00005

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.

Nothing to report

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.

Nothing to report

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

Over the next year we will continue our studies to develop reagents to overexpress or knockdown WT1, D88N-HSP90, HSP90AA, HSP90AB isoforms to assess changes in fibroblasts activation. These studies will help us to identify WT1- and Hsp90-specific gene networks and pathways in the pathogenesis of pulmonary fibrosis. This project will continue to test if combined therapy of 17-AAG and Pirfenidone attenuates fibrosis using mouse models of TGFα- and bleomycin-induced pulmonary fibrosis.

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).

IPF is a chronic and ultimately fatal disease in which tissue deep in the lungs becomes increasingly thick and stiff, or scarred, over time, making breathing more and more difficult. With the funding support from the DoD, our team identified that in IPF patients, activity of a particular protein, Hsp90 (Heat shock protein 90), is elevated in fibroblasts. Fibroblasts are cells in connective tissues that produce collagen and other fibers that have not yet progressed to form scar tissue. We also identified Hsp90 inhibitors as a potential effective therapy to stop or possibly even reverse the disease.

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 new findings demonstrate that Hsp90 is a positive regulator of fibroblast activation and ECM production. Increased Hsp90 activity and fibroblast activation has been shown in multiple organs undergoing fibrotic remodeling. Thus, the proposed studies will not only highlight the role of HSP90 activity in initiation and maintenance of pulmonary fibrosis, but also are essential to the development of novel therapeutics for the treatment of fibrosis in the lung and perhaps other organs. Nearly 45% of all deaths in the developed world are attributed to chronic fibroproliferative diseases, emphasizing the potential impact that an anti-fibrotic therapy would provide. Therefore, successful treatment that either reverses fibrosis or prevents disease progression would have an immediate and profound impact on healthcare.

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.*

CCHMC has filed a US provisional patent application (D14-0129) on the repurposing of 17AAG for IPF. The Center for Technology Commercialization (CTC) at CCHMC is in the process of initiating discussions with industry partners for joint development of this project after obtaining results of this project.

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

Remember that significant changes in objectives and scope require prior approval of the agency.

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.

Nothing to report

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.

Nothing to report

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

No changes to report

Significant changes in use or care of vertebrate animals

No changes to report

Significant changes in use of biohazards and/or select agents

No changes 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).*

Total three manuscripts have been accepted or under consideration for publication.

1. Vadde SR, **Madala SK** and Geereddy BR (2018) Extracellular small heat shock proteins: Exosomal biogenesis and function. ***Cell Stress & Chaperones*** 23(3):441-454. PMID: 29086335

2. Sontake V, Kasam RK, Debora S, Korfhagen TR, Geereddy BR, White ES, Jegga AG and **Madala SK** (2018) Wilms' Tumor 1 Drives Fibroproliferation and Myofibroblast Transformation in Severe Fibrotic Lung Disease. ***JCI insight*** 3(16) PMID: 30135315

3. Sontake V, Gajjala P, Kasam RK, and **Madala SK** (2018) New therapeutics based on emerging concepts in pulmonary fibrosis. ***Expert Opinion On Therapeutic Targets*** (in press)

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.*

1. Sontake V, Wang Y, Kasam RK, McCormack FK, Debora S, Geereddy BR, Naren AP, White ES, Jegga AG and **Madala SK** (2017) Hsp90 Regulation of Fibroblast Activation in Pulmonary Fibrosis. ***JCI insight*** 2: e91454. PMID: 28239659

2. Abstract titled **"Inhibition of fibroblast activation by integrating multiomics data and preclinical models of severe fibrotic lung disease"** presented at 2nd Annual IPF summit, San Francisco, August 20-22, 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.

News article titled "Computational Analyses Identify New Therapeutic Targets For Idiopathic Pulmonary Fibrosis" https://www.cincinnatichildrens.org/research/divisions/b/bmi/news/2017/2-27-computational-analyses-identify-new-therapeutic-targets-for-idiopathic-pulmonary-fibrosis

- **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: *Satish Madala*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *4*
Contribution to Project: *Dr. Madala, has performed work and analysis on fibroblast activation by Hsp90 and wrote the work reports and manuscripts.*
Funding Support:

Name: *Vishwaraj Sontake*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *6*
Contribution to Project: *Dr. Sontake has performed work and analyzed data on fibroblast activation by Hsp90.*
Funding Support:

Name: *Anil Jegga*
Project Role: *Associate Professor*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *2*
Contribution to Project: *Dr. Jegga has performed bioinformatics analysis 17-AAG and Wt1 effects on fibroblast activation.*
Funding Support:

Name: *Prathibha Gajjala*
Project Role: *Research Fellow*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *6*
Contribution to Project: *Dr. Gajjala has performed biochemical analysis of Hsp90 and in vivo studies.*
Funding Support:

Name: *Jaswath Yella*
Project Role: *Undergraduate Student*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *12*
Contribution to Project: *Jaswath has performed gene expression analysis under Dr. Jegga's supervision*
Funding Support:

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.*

Organization Name: University of Cincinnati
Location of Organization: (if foreign location list country) 51 Goodman Drive, Cincinnati, OH
Contribution to Project: Dr. McCormack has provided human samples and clinical perspective on IPF. The project staff have helped in collection and distribution of clinical samples.

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.*