

A. COMPONENT COVER PAGE

Project Title: Core C: Pre-Clinical Models of ARDS/VILI

Component Project Lead Information:

MORENO, VINASCO LILIANA

B. COMPONENT ACCOMPLISHMENTS**B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?**

Specific Aim #1: To provide a complete range of expertise, training, equipment, and data analysis tools to extensively study and characterize the role of cytoskeleton in preclinical models of murine lung injury.

Specific Aim #2: To house and care for the genetically-engineered mice and to generate novel transgenic and knockout mice.

Specific Aim #3: To examine selective siRNAs or pharmacological agonists or antagonists for cytoskeletal proteins as potential therapeutic strategies and approaches for ARDS and VILI models.

Specific Aim #4: To provide rigorously performed, protocol-driven performance of specific experimental strategies involving LPS and VILI preclinical models of ARDS/VILI as well as S1P and HGF rescue interventions.

Specific Aim #5: To evaluate the function of ARDS-associated SNPs and sites of functional protein post translational modification (PTM), utilizing mutated cDNA (high efficiency expression plasmids) targeting the lung endothelium (with ACE antibody conjugated liposome) in the endothelial conditional knockout mice.

Specific Aim #6: To provide high quality shared data for data storage and well-preserved lung tissue samples to individual projects for more sophisticated molecular and cellular assays.

RELEVANCE: ARDS is a devastating and life-threatening syndrome that most commonly occurs as a complication of severe infections and sepsis-induced ARDS is precipitated by an inflammation induced by lipopolysaccharide (LPS) or via ventilator-induced lung injury (VILI). This centralized Core has proven to be excellent on modeling lung injury for the purpose of studying underlying mechanisms and investigating strategies to prevent/treat ARDS studied in this PPG.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

Scientific publications.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Core C: In the final year of this PPG cycle, The Pre-Clinical Models of ARDS/VILI Core will continue to provide house and care for the genetically-engineered mice for each project. The Core will also assist Project Leaders with completion of key in vivo experiments utilizing the established murine models of lung injury. Furthermore, the Core will complete generation and characterization of various conditional KO mice in each Project including nmMLCK conditional KO mice and nmMLCK^{-/-} mice overexpressing endothelial-specific nmMLCK for Project #1, genetically-engineered heterozygous CTTN mice in Project #2, and integrin $\beta 4$ (ITGB4^{-/-}) mutant mice in Project #3. Lastly, the Core will continue strategies to assess SNP effects in KO mice exposed to murine inflammatory lung injury (ARDS/VILI) using SNPs-containing transgenes for key actin-binding protein genes (CTTN, EVL, ABL1). We will finalize the characterization of the nmMLCK conditional KO mice as well as the nmMLCK^{-/-} mice overexpressing endothelial-specific nmMLCK mice. Finally, we will complete and publish our manuscript defining the differential responses of our MYLK engineered mice using our ARDS or VILI models and/or two-hit model (LPS/VILI).

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

Program Project Title: Cytoskeletal Regulation of Lung Endothelial Pathobiology
Component Core Lead Name: Moreno-Vinasco, Liliana

Core C: Pre-Clinical Models of ARDS/VILI Core

Major Accomplishments: The Core C animal core has continued to provide high quality care for the genetically-engineered mice for each project. As detailed above, the Core has performed key experiments for the three projects utilizing our established murine models of lung injury (intratracheal instillation of LPS alone, VILI alone, and has developed the two-hit model (LPS and VILI simultaneously)) to allow publications by the PPG team. The Core has successfully developed the *nmMLCK*-conditional KO mice, bred genetically modified mice (*nmMLCK*^{-/-}) and *nmMLCK*^{-/-} mice overexpressing endothelial-specific nmMLCK for Project #1. The Core has also assisted Project #2 in utilizing the genetically-engineered heterozygous *CTTN* mice and over-expression strategies as therapeutic targets in murine inflammatory lung injury (ARDS/VILI) as well as SNPs-containing transgenes for key actin-binding protein genes (*CTTN*, *EVL*, *ABL1*). The Core has assisted Project #3 in ARDS studies (LPS and VILI model) in wild-type mice, integrin $\beta 4$ (*ITGB4*^{-/-}) mutant mice.

C. COMPONENT PRODUCTS**C.1 PUBLICATIONS**

Not Applicable

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT**E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?**

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS**F.3.a Human Subjects**

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Core-8098

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 806345617

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ARIZONA

Start Date*: 04-01-2020

End Date*: 03-31-2021

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Redacted by agreement					Core C Lead	Institutional Base Salary	EFFORT		20,335.00	6,385.00	26,720.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:		File Name:								Total Senior/Key Person		26,720.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Research Specialist	EFFORT			58,475.00	18,361.00	76,836.00
2	Total Number Other Personnel					Total Other Personnel	76,836.00
Total Salary, Wages and Fringe Benefits (A+B)							103,556.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 806345617

Budget Type*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ARIZONA

Start Date*: 04-01-2020

End Date*: 03-31-2021

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	0.00
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	0.00

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other:	
0 Number of Participants/Trainees	Total Participant Trainee Support Costs
	0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 806345617

Budget Type*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ARIZONA

Start Date*: 04-01-2020

End Date*: 03-31-2021

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		96,706.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		0.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
8. Animals (Background Mice)		8,000.00
9. 100 Cages Housing; Genotyping; Redacted by b6359682		35,000.00
Total Other Direct Costs		139,706.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	243,262.00

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1. Modified Total Direct Cost	53.5	243,263.00	130,146.00
Total Indirect Costs			130,146.00
Cognizant Federal Agency	DHHS, Jeanette Lu, 415-437-7820		
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	373,408.00

J. Fee	Funds Requested (\$)*
	0.00

K. Budget Justification*	File Name:
	(Only attach one file.)

RESEARCH & RELATED Budget (F-K) (Funds Requested)