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TITLE: A Phase 2 Study of Inhaled CO for the Treatment of ARDS

PRINCIPAL INVESTIGATOR: Augustine M.K. Choi, M.D.

CONTRACTING ORGANIZATION:
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New York, NY 10065-4805

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

We are conducting a multi-center, prospective, randomized, partially double-blind, placebo-controlled Phase II clinical trial of inhaled CO (iCO) for the treatment of ARDS. Our objective is to evaluate the safety, tolerability, and efficacy of low dose iCO (200 ppm) in patients with ARDS. One hundred intubated, adult subjects with ARDS will be randomized in a 1:1 ratio to receive either inhaled CO or inhaled air placebo for up to 90 minutes daily for a total of 5 consecutive days. The primary safety endpoint is to evaluate safety of inhaled CO by determining carboxyhemoglobin (COHb) levels and the incidence of pre-specified administration-related adverse events (AEs). The primary efficacy endpoint is the lung injury score (LIS) as measured on study days 1-5 and day 7. The secondary endpoint is to compare the effects of iCO versus placebo on biomarkers of mitochondrial dysfunction, inflammasome activation, and lipid mediators. All 5 sites have received approval from the USAMRMC Office of Research Protections (ORP) Human Research Protection Office (HRPO). All sites are activated for enrollment and are currently screening. One subject has been enrolled and completed 4 days of treatment.

15. SUBJECT TERMS
Acute Respiratory Distress Syndrome (ARDS)
Inhaled Carbon Monoxide (iCO)

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. INTRODUCTION:

Acute respiratory distress syndrome (ARDS) is a devastating disease affecting military, veteran, and civilian populations. ARDS is a syndrome of severe acute lung inflammation and hypoxemic respiratory failure affecting over 180,000 patients annually in the United States with overall mortality rates of 40%. Despite advances in critical care management and lung protective ventilation strategies, ARDS morbidity and mortality remain unacceptably high. The lack of specific effective therapies for ARDS indicates an urgent need for new treatments targeting novel pathways. Low dose inhaled carbon monoxide (iCO) is a novel therapeutic for ARDS supported by compelling data from experimental models of acute lung injury (ALI). We recently completed a Phase I, fixed dose escalation (100 ppm, 200 ppm) trial of iCO in sepsis-induced ARDS, which showed that precise delivery of low dose iCO is feasible and safe in mechanically ventilated ARDS patients. The objective of this study is to further assess safety and evaluate efficacy of low dose iCO therapy in mechanically ventilated patients with ARDS. This multi-center, prospective, randomized, partially double-blind, placebo-controlled Phase II clinical trial will enroll 100 intubated, adult patients with ARDS who will be randomized in a 1:1 ratio to receive either inhaled CO or inhaled air placebo for up to 90 minutes daily for 5 days.

2. KEYWORDS:

Acute Respiratory Distress Syndrome
Inhaled Carbon Monoxide (iCO)
Carboxyhemoglobin (COHb)
Coburn-Forster-Kane Equation
Lung Injury Score
Mitochondrial Dysfunction
Inflammasome
Lipid Mediators

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The overall goal is to conduct a randomized, placebo-controlled Phase II study of low dose iCO for the treatment of ARDS.

The specific aims are: 1) to evaluate the safety, tolerability, and efficacy of low dose iCO in patients with ARDS, and 2) to investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS.

Specific Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS. *Hypothesis: Low dose iCO will be safe and well-tolerated and will reduce the severity of lung injury and nonpulmonary organ failure in ARDS patients.* We will conduct a Phase II randomized, double-blind, placebo-controlled trial of low dose iCO in mechanically ventilated patients with ARDS. We will enroll 100 adult patients with ARDS (based on 85% power to detect a difference in lung injury score [LIS]) and randomize subjects to iCO or placebo (medical grade air) treatment with a 1:1 randomization scheme.

Specific Aim 2: To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS. *Hypothesis: Low dose iCO will reduce mitochondrial dysfunction, attenuate inflammasome activation, and promote resolution of inflammation in ARDS patients.* We will measure plasma levels of mitochondrial DNA, autophagy markers, inflammasome components, and lipid mediators in subjects pre- and post-treatment with iCO or placebo. We will determine whether CO modulates these novel pathways and evaluate if

these candidate biomarkers correlate with clinical efficacy endpoints in ARDS patients in the Phase II trial.

Major Tasks and Percent Completion:
Major Task 1: Prepare CO in ARDS Protocol for Implementation- Months 1-4
In year 1 of this project we have completed 100% of Major Task 1.

Major Task 2: Coordinate Study Staff for Clinical Trial, Subtask 1: Hiring and Training of Study Staff- Months 1-5
In year 1 of this project we have completed 98% of Subtask 1, Major Task 2.

Major Task 3: Prepare Study Related Documents, Equipment, and Procedures- Months 1-4
In year 1 of this project we have completed 100% of Major Task 3.

Major Task 4: Participant Recruitment, Therapy, Participant Evaluation- Months 4-46
Screening and recruitment has been initiated in the intensive care units (ICUs) at all 5 participating sites.

Major Task 5: Biomarker Assays and Statistical Analysis- Months 6-50
Work has not begun on Major Task 5.

What was accomplished under these goals?

Major Task 1: Prepare CO in ARDS Protocol for Implementation

- The study protocol and informed consent form were finalized and approved by the Data and Safety Monitoring Board (DSMB).
- Clinical Trial Agreements have been executed for all 5 participating sites.
- An IND amendment was submitted to the FDA on September 10, 2018, including an updated General Investigational Plan, CO ARDS Phase II Protocol, and Investigator's Brochure, v. 3.0, 9/3/2018.
- HRPO approval has been obtained for all 5 sites.
- Approval of Protocol v.3.0 has been obtained from all site IRBs.
- Approval of Protocol v.4.0 has been obtained from the IRBs at WCM, BWH, MGH, and Duke, and is pending approval at Durham VA.

Site	Initial IRB approval	HRPO Approval
WCM	10/31/2018	4/26/2019
BWH	11/8/2018	4/26/2019
MGH	11/8/2018	4/26/2019
Duke	1/24/2019	7/29/2019
Durham VA	3/12/2019	7/29/2019

Major Task 2: Coordinate Study Staff for Clinical Trial, Subtask 1: Hiring and Training of Study Staff

- The following trainings have been completed for investigators and study staff:
    - CO ARDS Phase II Study Training Webinar on Protocol v.3.0, study equipment, adverse event reporting, and study database, held on 5/1/2019 for all investigators and study staff.
    - Coordinator Training Webinar, held on 5/15/2019 and 6/7/2019.

- GEM 5000 Training, held on 2/6/2019 and 7/24/2019 for all respiratory therapists and unblinded investigators.
- On-site COVent Delivery System training for all respiratory therapists and unblinded investigators, held on 3/19/2019, 3/20/2019, and 3/21/2019.

Major Task 3: Prepare Study Related Documents, Equipment, and Procedures

- The DSMB Charter and Statistical Analysis Plan (SAP) were finalized and approved by the DSMB as of 2/17/2019.
- The StudyTrax database has been finalized and is live for data entry.
- The Manual of Operations (MOP) was finalized as of 5/8/2019 and distributed to all sites.
- All 5 sites have the following equipment on site for the study:
  - 2 COVent Delivery systems from 12th Man Technologies
  - 1 GEM 5000 Co-oximeter from Instrumentation Laboratory (Werfen)
  - 1 Masimo Radical-7 Pulse Oximeter
  - 1 NM3 or NICO Monitor
  - 1 Drager Pac 7000 CO Detector
- Equipment Standard Operating Procedures (SOPs) for all of the above equipment were created and distributed to all the sites.
- Study Drug and Calibration Cylinders from Praxair have been received at all 5 sites. Drug accountability logs have been distributed to all sites and a Master Accountability Log is on file.
- A CO ARDS Phase II Lab Manual, Sample Collection Forms, and Sample Labels were created and distributed to all the sites.

Major Task 4: Participant Recruitment, Therapy, Participant Evaluation

- All sites have completed a Site Initiation Visit and have been activated for recruitment.
- Screening of the ICUs has started at all sites.
- One participant was enrolled at BWH on 9/30/2019.
- The most common exclusion criteria include:
  - Severe hypoxemia defined as $SpO_2 < 95$ or $PaO_2 < 80$ on $FiO_2 \geq 0.8$ (22% of patients)
  - Greater than 120 hours since ARDS onset (22% of patients)
  - Moribund patient not expected to survive 24 hours (17% of patients)
  - Concomitant use of inhaled pulmonary vasodilator therapy (17% of patients)

Site	Activation Date	Pre-screened subjects	Met inclusion criteria	Had an exclusion	Enrolled
BWH	6/24/2019	34	12	11	1
WCM	7/1/2019	23	4	4	0
MGH	8/1/2019	11	5	5	0
Duke	9/20/2019	10	3	3	0
Durham VA	9/20/2019	0	0	0	0

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

Title: Review of Chest X Rays– Practice session for identifying ARDS
Led by Dr. Taylor Thompson
Date: 8/20/2019
Attendees: Principal investigators, study coordinators, treating physicians.

How were the results disseminated to communities of interest?

Nothing to report.

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

To accomplish the goals of the study, in the next reporting period, we plan to:

- Continue screening, and enroll and randomize 51 participants across all sites by the end of Year 2.
- Conduct long-term outcome training for study coordinators in conjunction with Dr. Dale Needham's group at Johns Hopkins.
- Perform quality control and quality assurance activities, including conducting site monitoring visits.
- Ongoing collection of participant study data and specimen collection.
- Perform biomarker assays.

4. IMPACT:

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

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Not applicable.

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

There was a delay in site activation and initiation of screening due to the time required for HRPO approval. The delivery of the study product from the manufacturer Praxair also delayed the trial start. All sites are now activated and actively screening. To enhance recruitment and retention of study participants, we will actively engage our clinical communities. We will raise awareness of our Phase II trial by educating housestaff, critical care fellows, ICU staff and attendings on the rationale and design of our study, as well as the eligibility criteria for enrollment. We will meet with the ICU fellows, nursing staff, and attendings to review the study protocol and provide educational material on the trial. Investigators at each of the participating sites have strong commitment from their ICU directors and enthusiastic institutional support.

We have developed a pre-specified plan for monitoring enrollment at the sites along with potential corrective actions. The Data Coordinating Center (DCC) will monitor screening and recruitment at each of the participating sites. The DCC will regularly review enrollment at 3 months and 6 months after study initiation, followed by reviews every 3 months, depending on whether additional reviews

are triggered by low enrollment. Certain levels of enrollment at each site may trigger the DCC to contact the site for a review of screening and enrollment procedures.

While there are currently no competing trials at any of our sites, one potential limitation to enrollment in our Phase II study may be competing trials at some of our participating sites. While we view having the infrastructure and expertise to conduct ARDS trials at each of our sites as strengths, it is possible that competing trials could reduce subject enrollment in our study. Each participating center currently has a screening algorithm in place to equally distribute potentially eligible patients across trials that have similar enrollment criteria, with priority given to Department of Defense and NIH-funded studies. In addition, co-enrollment of participants in more than one trial may be allowed in specific instances (*eg*. observational studies). If patient accrual is slow or enrollment below goal, we will consider adding additional affiliated hospitals, and may need to add additional sites from the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network.

We will also implement several engagement strategies to ensure retention of study participants for assessment of long-term outcomes following hospitalization. We will work closely with Dr. Dale Needham at Johns Hopkins University, who has extensive expertise with long-term outcomes assessment after acute respiratory failure and critical illness, including strategies to maximize patient cohort retention for longitudinal long-term outcomes research studies.

Changes that had a significant impact on expenditures
Not applicable.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Not applicable.

Significant changes in use or care of human subjects
Not applicable.

Significant changes in use or care of vertebrate animals
Not applicable.

Significant changes in use of biohazards and/or select agents
Not applicable.

6. PRODUCTS:

Publications, conference papers, and presentations
Nothing to report.

- **Journal publications.**
  Nothing to report.

- **Books or other non-periodical, one-time publications.**
  Nothing to report.

- **Other publications, conference papers and presentations**.
  Nothing to report.

Website(s) or other Internet site(s)

ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT03799874

A description of the study is provided and includes the following sections: study design, arms and interventions, outcome measures, eligibility criteria, and contact information.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

A database for the study has been designed in StudyTrax, a 21 CFR Part 11-compliant data capture system that has the capacity for data entry and transfer from a wide variety of existing databases, tracking data manipulation and export into standard statistical packages, as well as advanced dataset analysis.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Weill Cornell Medicine

Name: **Augustine Choi**
Project Role: Principal Investigator
eRA Commons ID: CHOIAM
Nearest person month worked: 1.812
Contribution to Project: Dr. Choi is overseeing the research proposal and the overall planning and execution of the clinical trial grant. He contributed to the overall design of the study and oversaw the coordination of sites for the institutional IRB submissions and the advancement of the study according to the timeline.

Name: **Maria Plataki**
Project Role: Site PI/ Co-Investigator
eRA Commons ID plataki
Nearest person month worked: 6.0
Contribution to Project: Dr. Plataki has overseen the IRB submission and approval at Weill Cornell, has helped coordinate the proposed trial activities, and has facilitated the trial start-up at Weill Cornell including supervising availability and preparation of trial-related equipment. Dr. Plataki is overseeing screening and enrollment of subjects at WCM, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data.

Name: **Mary Choi**
Project Role: Co-Investigator
eRA Commons ID CHOIME
Nearest person month worked: 1.2
Contribution to Project: Dr. Choi's effort was devoted to participating in study design, assisting with study start-up and obtaining IRB approval at Weill Cornell.

Name: **Robert Winchell**
Project Role: Co-Investigator
eRA Commons ID rwinchell
Nearest person month worked: 0.24
Contribution to Project: Dr. Winchell's effort was spent in study start-up and preparation for screening in the trauma and burn ICUs.

Name: **Elizabeth Peters**
Project Role: Project Manager
eRA Commons ID
Nearest person month worked: 3.96
Contribution to Project: Ms. Peters has assisted with the trial start-up including IRB, IND, and DoD HRPO submissions, design of the case report forms, and development of the study database, and is overseeing the advancement of the study according to work plan and timeline.

Name: **Luis Gomez-Escobar**
Project Role: Research Coordinator
eRA Commons ID
Nearest person month worked: 12
Contribution to Project: Dr. Gomez-Escobar has replaced Elizabeth Sanchez as the Research Coordinator at Weill Cornell. He has completed study training and has recently started screening the ICUs for potential participants meeting study eligibility criteria.

Name: **Michelle LoPiccolo**
Project Role: Project Administrative Coordinator
eRA Commons ID
Nearest person month worked: 3.84
Contribution to Project: Ms. LoPiccolo is liaising with participating sites to ensure proper communication regarding the project. She is responsible for scheduling conference calls, assists with scheduling of training sessions and purchasing all necessary materials related to training.

Brigham and Women's Hospital

Name: **Laura Fredenburgh**
Project Role: Site PI/ Co-Investigator
eRA Commons ID: LF1234
Nearest person month worked: 2.4
Contribution to Project: Dr. Fredenburgh has directed the overall design and writing of the Phase II study protocol, coordinated with the sites for IRB submissions, and submitted the IND amendment to the FDA. Dr. Fredenburgh has directed the trial start-up including developing materials to conduct the study, purchasing trial-related equipment, as well as developing the case report forms and database design. Dr. Fredenburgh is overseeing screening and enrollment of subjects at BWH, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data.

Name: **Rebecca Baron**
Project Role: Co-Investigator/DCC Co-Director
eRA Commons ID: rmb123
Nearest person month worked: 3.0

Contribution to Project: Dr. Baron has assisted with developing materials to conduct the study, participated in the study design, and assisted with development of the case report forms and the statistical analysis plan. Dr. Baron is co-directing the DCC and overseeing regulatory reporting for the trial in conjunction with Dr. Taylor Thompson.

Name: **Mark Perrella**
Project Role: Co-Investigator/IND Sponsor
eRA Commons ID: map123
Nearest person month worked: 1.2
Contribution to Project: Dr. Perrella has assisted with the study design, IND amendment submission to the FDA, and trial start-up activities including development of trial-related materials. Dr. Perrella is assisting with enrollment, treatment, and collection of clinical data from enrolled subjects in the trial.

Name: **Souheil El-Chemaly**
Project Role: Co-Investigator
eRA Commons ID: elchemalys
Nearest person month worked: 0.6
Contribution to Project: Dr. El-Chemaly is the Independent Research Monitor and has assisted with trial start-up including assisting with the study protocol design and study monitoring plan. Dr. El-Chemaly will independently evaluate all safety and monitoring data from the trial on a quarterly basis and report his findings to the IND Sponsor, PI, USAMRMC HRPO, as well as the site PIs.

Name: **Peter Hou**
Project Role: Co-Investigator
eRA Commons ID: peterhou
Nearest person month worked: 0.24
Contribution to Project: Dr. Hou has participated in trial start-up and development of materials to conduct the study. Dr. Hou will serve as a blinded investigator to adjudicate adverse events (AEs) at BWH. He will review all AEs and assess their relationship to the study intervention.

Name: **Rie Maurer**
Project Role: Statistician
eRA Commons ID:
Nearest person month worked: 2.1
Contribution to Project: Ms. Maurer has participated in the Phase II study design including power calculations and preparation of the randomization schedule, as well as development of the Statistical Analysis Plan. Ms. Maurer will assist with quarterly reporting to the DSMB and data analysis of the study endpoints.

Name: **Ana Patricia Saade Lemus**
Project Role: Project Manager
eRA Commons ID: asaadelemus
Nearest person month worked: 12
Contribution to Project: Dr. Saade Lemus has assisted with the trial start-up including IRB and IND submissions, design of the case report forms, and development of the study database. She is currently screening subjects for enrollment at BWH.

Name: **Alexis Corcoran**
Project Role: Research Assistant

eRA Commons ID:
Nearest person month worked: 6.0
Contribution to Project: Ms. Corcoran is assisting with trial start-up activities including purchasing and maintaining trial-related supplies including blood collection tubes and cryovials for biospecimen processing and storage. Ms. Corcoran is assisting will processing clinical samples from enrolled subjects and managing samples from the participating sites in a central biorepository at BWH.

Name: **Yao-Wen Kuo**
Project Role: Research Assistant
eRA Commons ID:
Nearest person month worked: 0
Contribution to Project: Dr. Kuo is assisting with calibration and maintenance of trial-related study equipment.

Name: **Charles Serhan**
Project Role: Other Significant Contributor
eRA Commons ID: CNSERHAN
Nearest person month worked: 0
Contribution to Project: Dr. Serhan is providing his expertise in lipid mediators and specialized pro-resolving mediators in resolution biology. He will oversee metabololipidomic profiling assays from biospecimens collected from enrolled subjects.

Massachusetts General Hospital (The General Hospital Corp.)

Name: **Marcos Vidal Melo**
Project Role: Site PI
eRA Commons ID: MVMELO
Nearest person month worked: 2.4
Contribution to Project: Dr. Vidal Melo supervised the trial management team at MGH including preparations associated with the research coordinator and respiratory therapists. Dr. Vidal Melo oversaw the preparation of facilities, personnel and equipment for screening and enrollment of subjects, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data.

Name: **B. Taylor Thompson**
Project Role: Co-Investigator/ DCC Co-Director
eRA Commons ID: BTTHOMPSON
Nearest person month worked: 1.2
Contribution to Project: Dr. Thompson has assisted with developing materials to conduct the study, participated in the study design, and assisted with development of the case report forms and the statistical analysis plan. Dr. Thompson is participating in the oversight of the trial including screening and enrollment, randomization, data collection and auditing, adverse event reporting, and report generation for the FDA, HRPO, and the DSMB.

Name: **Noelle Saillant**
Project Role: Co-Investigator
eRA Commons ID: N3SAILLANT
Nearest person month worked: 0.24
Contribution to Project: Dr. Saillant participated in preparing the conduct of the project in the trauma and burn ICUs at MGH.

Name: **Mammary Kone**
Project Role: Clinical Research Coordinator
eRA Commons ID: mamarykone
Nearest person month worked: 3.0
Contribution to Project: Mr. Kone participated in preparing documentation, equipment, and facilities; IRB submission; communication with the DCC in preparation for the implementation of the study. Mr. Kone is actively screening subjects for enrollment in the study at MGH.

Name: **Katherine Luchette**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 3.0
Contribution to Project: Ms. Luchette participated in preparing documentation, equipment, and facilities; IRB submission; communication with the DCC in preparation for the implementation of the study. Ms. Luchette is actively screening subjects for enrollment in the study at MGH.

Name: **Dean Hess**
Project Role: Consultant
eRA Commons ID: ARCFHESS
Nearest person month worked: 50 hours per year
Contribution to Project: Mr. Hess is serving as a consultant for the project as a senior respiratory therapist on topics regarding the implementation of the protocol for monitoring and delivering CO to mechanically ventilated subjects. Mr. Hess has been assisting with training of local investigators regarding preparation of equipment and personnel for the trial.

Duke University & Institute for Medical Research, Inc.

Name: **Karen Welty-Wolf**
Project Role: Site PI/ Co-Investigator
eRA Commons ID: welty001
Nearest person month worked: 3.0
Contribution to Project: Dr. Welty-Wolf, the Duke and Durham VA Medical Center Site Director, is responsible for supervision and implementation of all aspects of the study at Duke Hospital and the Durham VA Hospital. During this year, Dr. Welty-Wolf's effort was devoted to supervision of study start-up, obtaining IRB approval, and subaward administration at both sites.

Name: **Claude Piantadosi**
Project Role: Co-Investigator
eRA Commons ID: CA_PIANTADOSI_MD
Nearest person month worked: 3.0
Contribution to Project: Dr. Piantadosi is assisting with implementation of the study at Duke Hospital. During this year, Dr. Piantadosi's effort was devoted to supervision of study start-up, obtaining IRB approval, and subaward administration.

Name: **Corey Vatsaas**
Project Role: Co-Investigator
eRA Commons ID: CVATSAAS
Nearest person month worked: 0.24
Contribution to Project: Dr. Vatsaas is preparing for recruitment of subjects in the Duke surgical and trauma ICU populations and assisting with study drug administration in those subjects.

During this year, Dr. Vatsaas' effort was spent in study start-up and preparation for screening in the surgical ICUs.

Name: **Bryan Kraft**
Project Role: Co-Investigator
eRA Commons ID: bryankraft
Nearest person month worked: 2.4
Contribution to Project: Dr. Kraft is responsible for conducting and analyzing biomarker studies for mitochondrial Quality Control on isolated blood leukocytes. He will also assist with data collection and administration of the study drug. During this year, Dr. Kraft's efforts concentrated on study start-up.

Name: **John Davies**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 4.0
Contribution to Project: Mr. Davies is a Registered Respiratory Therapist and will supervise CO study gas administration. He will be responsible for CO device calibration, performance testing, and continuous maintenance of study equipment. He will also be responsible for education and training of respiratory therapists across all study sites in equipment use and calibration and for study drug administration, and he will provide on call support to all sites for any issues that arise during implementation of the study protocol. During this year, Mr. Davies worked on study start-up, including equipment preparation and education and training of respiratory therapists in CO administration in preparation for study subject enrollment.

Name: **Mona Malik**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 12.0
Contribution to Project: Dr. Malik is responsible for study screening, subject enrollment, and management of clinical data, study records, and regulatory processes at two study sites, Duke Hospital and the Durham VA Hospital. During this year, Dr. Malik's efforts were devoted to obtaining IRB approvals at Duke Hospital and the Durham VA Hospital.

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

See the enclosed updated Other Support pages for the key personnel on this project.

What other organizations were involved as partners?

Nothing to report.

PREVIOUS/CURRENT/PENDING SUPPORT: CHOI, M.K. AUGUSTINE

ACTIVE GRANTS

P01 HL114501 (Choi) 09/06/2013 – 06/30/2020 (NCE) Core A: 0.12 calendar months; Project 1: 0.12 calendar months
Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers
Direct Cost: $234,935 (Proj 1) $51,015 (Core A)
Role: Overall PD/PI; Project 1 Leader; Core A Leader
Name and address of Contracting/Grants Officer: Dr. Antonello Punturieri, Division of Lung Diseases; National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: In this program project we have integrated the expertise of investigators from COPD and IPF community, both basic and translational, to come together to better understand the pathogenesis of these chronic lung diseases, and hopefully identify new molecular targets in the treatment of these dreadful diseases in the future.
Specific Aims: We will attempt to reach our goals by the addressing the following projects and cores: **Project 1) Homeostatic Role of Autophagy in Lung Emphysema and Fibrosis: Specific Aim 1:** Determine whether divergent regulation of autophagy in fibrosis and emphysema is TGF-β1 dependent or independent **Specific Aim 2:** Determine whether autophagy mediates emphysematous and/or fibrotic responses via mTOR independent or dependent pathway **Specific Aim 3:** Determine the role of mitochondria derived reactive oxygen species (ROS) and mitophagy in the development of emphysema or pulmonary fibrosis; **Project 2) Genetic Modifiers of TGF-Beta1 and Cigarette Smoke in Fibrosis and Emphysema- Specific Aim 1:** Define the roles of Wisp-1, Lama1, Sfn, and Plunc in the pathogenesis of TGF-β1-induced fibrosis. **Specific Aim 2:** Define the roles of Ccna2 and PAI-1 in the pathogenesis of TGF-β1-induced injury and emphysema. **Specific Aim 3:** Characterize the effects of CS on TGF-β1-induced fibrosis and emphysema, the expression of the genetic modifiers of these responses and DNA methylation. **Specific Aim 4:** Characterize the expression of TGF-β1 genetic modifiers in tissues from patients with IPF or COPD. **Project 3) Genetics and Epigenetics of COPD and IPF- Specific Aim 1:** Rare Genetic Determinants of COPD and ILD **Specific Aim 2:** Epigenetic Determinants of COPD and ILD **Specific Aim 3:** System Genetics; **Project 4) Clinical Outcomes and Molecular Phenotypes in Smokers with Parenchymal Lung Disease- Specific Aim 1:** Define the chest CT patterns that predict functional impairment in smokers with ILA and how they impact the clinical progression of patients with COPD **Specific Aim 2:** Demonstrate divergent regulation of TGF-β1 related molecular pathways in smokers with ILA and IPF patients when compared to patients with COPD **Specific Aim 3:** Identify divergent regulation of novel alveolar macrophage and epithelial cell gene networks in smokers with ILA and patients with IPF and COPD. **Core 1) Administrative Core**- The core will provide administrative support for budgetary and personnel resource management, coordination of regular scientific and review meetings, and regulatory and scientific reporting of the research activities. **Core 2) Respiratory Computational Discovery Core**- The studies proposed in this program project will generate a series intricate datasets consisting of a variety of data types, including extensive clinical phenotypes, genome-wide genotypes, gene expression and methylation data. **Core 3) Clinical Biorepository Core**- This core aims to recruit, phenotype and sample IPF and COPD patients, smokers with interstitial lung abnormalities and smokers without lung disease. The core will coordinate all human samples (BAL samples, lung tissues, cells) which will be used by all projects of the PPG; **Core 4) Murine Models and Molecular Analysis Core**- The core will

provide projects based at BWH with the expertise and resources required for CS induced emphysema and bleomycin and irradiation induced fibrosis in mice. The core will also provide molecular analysis for clinical projects of the PPG.
Overlap: None

R01 HL060234 (M. Choi/ A.M.K Choi - Multi-PI) 03/14/2014-1/31/2019 (NCE) 0.12 calendar months
NIH/NHLBI
Heme Oxygenase-1/Carbon Monoxide in Lung Vascular Injury
Direct Cost: $299,779
Role: Co-PI
Name and address of Contracting/Grants Officer: Lei Xiao, M.D., Ph.D., Program Director & Medical Officer, National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: The major goal of this project is to determine the role of autophagy in pulmonary hypertension (PH). The project explores how autophagy represents an adaptive stress response to protect against PH, and that CO prevents PH via regulating autophagy. We also explore whether autophagy regulated inflammasomes can potentially serve as diagnostic biomarker in predicting severity of PH.
Specific Aims: We will test the hypothesis by addressing the following aims: **Aim 1:** To determine the mechanism by which CO-induced autophagy functions to provide cytoprotection in experimental PH.
Aim 2: To determine the mechanism by which CO dampens the inflammasome pathway in experimental PH. **Aim 3:** To determine whether CO inhibits inflammasome and its regulated cytokines
in human PH.
Overlap
none

R01 HL055330-20 (A. Choi/M. Choi – Multi-PI) 4/1/2018-3/31/2022 1.2 calendar months
NIH/NHLBI
Inflammasomes: Regulation and Function in Acute Lung Injury
Direct Costs: $299,995
Role: Co- PI (Contact)
Name and address of Contracting/Grants Officer: Lora Reineck, M.D., M.S., Medical Officer, Division of Lung Diseases/ National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: The overall goal is to understand the role of receptor-interacting protein-3 kinase (RIPK3)-dependent necroptosis pathway and inflammation in the pathogenesis of experimental acute lung injury (ALI) and in human disease such as ARDS. The project examines how mechanical injury or infection causes dysregulated fatty acid (FA) metabolism resulting in activation of RIPK3-dependent signaling and necroptosis, and that disruption of FA metabolism promotes macrophage inflammasome activation and pro-inflammatory cytokines production, which contributes to the development of ALI. We also determine whether necroptosis-related proteins and FA are associated with morbidity and mortality in patients with critical illness, including ARDS.
Specific Aims: Aim 1: To determine the regulation and function of RIPK3-dependent necroptosis in ALI. **Aim 2:** To determine the mechanisms by which necroptosis mediates NOX4-dependent

NLRP3 inflammasome activation in ALI. **Aim 3:** To determine the clinical relevance of necroptosis and FA metabolism in the critically ill patients, including ARDS.

Overlap

none

R01 HL132198 (A. Choi/M. Choi - Multi-PI) 01/01/2017-12/31/2020 0.912 calendar months

NIH/NHLBI

Metabolic dysfunction regulates mitophagy-dependent necroptosis in COPD

Direct Cost: $326,474

Role: Co-PI (Contact)

Name and address of Contracting/Grants Officer: Lisa Postow, Ph.D., Program Director, National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952

Goals: The goal is to examine activation of mitophagy-dependent necroptosis pathway in response to metabolic and mitochondrial dysfunction that may adversely affect airway function and emphysema outcomes during CS-induced COPD pathogenesis.

Specific Aims: Aim 1: To determine the mechanisms by which CS induces mitophagy in the lung.

Aim 2: To determine the effect of impaired OXPHOS and FA synthesis on the regulation of mitochondrial dynamics and biogenesis and their impact on experimental COPD. **Aim 3:** To determine the regulation of cellular necroptosis by CS-dependent mitophagy, and its impact on lung functional impairment in experimental models of COPD.

Overlap

none

R01 HL133801 (M. Choi/ A. Choi - Multi-PI) 08/01/2017-07/31/2021 1.2 calendar months

NIH/NHLBI

Novel role of RIPK3-dependent necroptosis pathway in lung and kidney fibrosis

Direct Cost: $338,183

Role: Co-PI

Name and address of Contracting/Grants Officer: Matt Craig, Ph.D., Program Director, National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952

Goals: The goal of this project is to understand the role of receptor-interacting protein-3 kinase (RIPK3) and its signaling target the mixed lineage kinase domain-like protein (MLKL) in the pathogenesis of organ fibrosis. We explore RIPK3 as a novel mediator of organ fibrosis with differential organ or tissue-specific effects through MLKL-independent and MLKL–dependent pathways in experimental models of kidney and lung fibrosis using unilateral ureteral obstruction (UUO)-induced kidney fibrosis, and in bleomycin-induced pulmonary fibrosis. We also explore whether the endogenous gaseous molecule carbon monoxide (CO) confers protection against multi-organ fibrosis by targeting either RIPK3 and/or FA-dependent pathways. RIPK3 and/or FA-biosynthetic proteins potentially serve as diagnostic biomarkers in predicting the severity of organ fibrosis and the efficacy of CO therapy.

Specific Aims: Aim 1: To characterize the function of RIPK3 and MLKL in the pathogenesis of organ fibrosis; **Aim 2:** To determine the pathogenic contribution of RIPK3-regulated fatty acid (FA) synthesis in fibrotic organs; **Aim 3:** To determine the role of the RIPK3 and the FA synthesis pathways in the therapeutic effects of CO in experimental lung and kidney fibrosis, and in human fibrosis.

Overlap
none

W81XWH1810667 (A. Choi) 09/15/2018 – 09/14/2022 1.812 calendar months
Department of Defense
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Role: Co-Investigator
Direct Costs: $2,446,383
Name and address of Contracting/Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Goals: The major goal of this phase II study is to evaluate safety, tolerability, and efficacy of inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS.
Overlap: None

GRL Phase II (Yoon) 03/01/2019-02/28/2022 0.24 calendar months
National Research Foundation of Korea
Development of predictive biomarkers for refractory allergic airway disease
Role: PI
Direct Costs: $72,703/DC
Name and address of Contracting/Grants Officer: Yonsei University College of Medicine, having an office at 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
Goals: The purpose of the joint research shall be i) to discover biomarkers predictive of subclinical allergic rhinitis (SAR) and/or allergic rhinitis (AR) in normal subjects, as well as the progression of AR to nasal polyps (NP) or allergic asthma (AA), ii) to outline regulatory mechanisms for any biomarkers found to be predictive of SAR and/or AR, and progression of AR to NP or AA using mouse models and cell culture systems, and iii) to validate the use of any identified biomarkers through a long-term longitudinal study of identical patients.
Specific Aims: Aim 1: to discover biomarkers predictive of subclinical allergic rhinitis (SAR) and/or allergic rhinitis (AR) in normal subjects, as well as the progression of AR to nasal polyps (NP) or allergic asthma (AA), **Aim 2:** to outline regulatory mechanisms for any biomarkers found to be predictive of SAR and/or AR, and progression of AR to NP or AA using mouse models and cell culture systems, and **Aim 3:** to validate the use of any identified biomarkers through a long-term longitudinal study of identical patients.
Overlap: None

T32HL134629 (A.Choi/F.J. Martinez) 02/01/2018-01/31/2023 0 calendar months
NIH/NHLBI
Multidisciplinary Approach Training in Respiratory Research
Role: Co-PI
Direct Costs:
Name and address of Contracting/Grants Officer: Laurel Katherine Kennedy Email: laurel.kennedy@nih.gov Phone: 301-827-4777. National Heart, Lung, and Blood Institute, 6701 Rockledge Drive Room 7044 Bethesda, MD 20892-7926
Goals: This program in pulmonary and critical care medicine provides comprehensive research training for individuals with a firm commitment to a career in research focused on lung disease. Our major goal is to train future physician scientists and scientists to become independent researchers in academic medicine. This T32 program will enable our fellows to have a better understanding of the pathogenesis of lung disease and to identify new therapeutic modalities in pulmonary disease

Overlap: None

PENDING SUPPORT

R61/R33 (A. Choi/ L. Fredenburgh - Multi-PI) 07/01/20 – 06/30/24 3.24 calendar months YR1, 3.0 calendar months YR2-4
NIH/NHLBI
A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Role:
Name and address of Contracting/Grants Officer Lora Reineck (lora.reineck@nih.gov)
Funding Amount: $ 348,291
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

P01 HL114501 (Choi) 04/01/2020-03/10/25 0.6 calendar months Core A/2.4 calendar months Project 1
NIH/NHLBI
Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers
Role: Overall PD/PI; Project 1 Leader; Core A Leader
Direct Costs: $212,924 (Proj 1) $76,870 (Core A)
Name and address of Contracting/Grants Officer: David Goff, M.D. National Heart, Lung, and Blood Institute (NHLBI) Telephone: 301-435-0422 Email: NHLBI_DCVS500k@mail.nih.gov
Goals: In this program project we have integrated the expertise of investigators from COPD and IPF community, both basic and translational, to come together to better understand the pathogenesis of these chronic lung diseases, and hopefully identify new molecular targets in the treatment of these dreadful diseases in the future.
Specific Aims: Project 1) Mitochondrial Dysfunction and Metabolic Regulation of the Necroptosis Pathway in COPD and IPF: Aim 1: To determine the functional significance of PINK1-regulated RIPK3 signaling in fibrosis and emphysema. **Aim 2:** To determine the mechanism(s) by which mitochondrial and metabolic pathways regulate PINK1-RIPK3 signaling in CS induced fibrosis and emphysema. **Aim 3:** To evaluate whether circulating cf-mtDNA and RIPK3 are associated with severity and progression of ILD and COPD. **Project 2) Differential Roles of Chi3l1 and its receptors in COPD and IPF: Aim 1:** Characterize the relationships between the fibrosis-associated and emphysema-associated TGF-1 genetic modifiers and Chi3l1 and its receptors in the lung at baseline, after exposure to CS or TGF-β1 and in models of

pulmonary fibrosis and emphysema. **Aim 2:** Characterize the site, mechanism and consequences of Chi3l1 activation/deactivation mediated through CDK and PP2A/FAM13A interaction. **Aim 3:** Characterize the importance of IL-13Rβ2 glycosylation and epigenetic modifications of IL-13Rβ2 and TMEM in the trafficking, binding and effector responses of Chi3l1. **Aim 4:** Characterize the interactions between the Chi3l1 axis and mitochondria. We will evaluate the regulation of Chi3l1 and its receptors by the RIG-I-like helicase (RLH) pathway and mitochondrial pathways involving PINK 1, Mfn1, Mfn2, and fatty acid synthase (FASN). We will also determine if Chi3l1 regulates mitochondrial function, dynamics such as fission and fusion and mitochondrial biogenesis and mitophagy. **Project 3) Integrating Omics, Networks, and Functional Studies in COPD and IPF: Aim 1:** Association of Chitinase and Mitochondrial Pathway Proteins with Human COPD and IPF. **Aim 2:** Network and Systems Analysis of Human COPD and IPF. **Aim 3:** Functional Validation of Biological Networks in COPD and IPF. **Project 4: Integrative Genomics of COPD and IPF: Aim 1:** Cell specificity in human COPD and IPF. **Aim 2:** Single cell RNA-sequencing in mouse models. **Aim 3:** Drug targets for COPD and IPF. **Core A) Administrative Core: Aim 1:** To provide administrative support for the coordination of regular scientific and review meetings. **Aim 2:** To provide administrative support for regulatory and scientific reporting of the research activities. **Aim 3:** To provide administrative support for budgetary and personnel resource management**. Aim 4:** To provide and coordinate all administrative activities between the participating PPG institutions: Weill Cornell Medicine, Brigham and Women's Hospital, Harvard School of Public Health, and Brown University. **Core B) Respiratory Computational Discovery Core: Aim 1:** Provide support and guidance for experimental design and data management relevant to the various -Omics technologies and the data PPG investigators will generate, including guidance on data reporting consistent with MIAME, dbGaP, and other relevant standards, and ensure adherence to NIH data sharing policies. **Aim 2:** Develop and apply methods to infer gene regulatory networks integrating multi-Omic data. We will use those networks to explore the regulatory processes altered in the progression from health to disease, between disease states, and between male and female patients. And we will work with the Project teams to integrate the results from these analyses with data on drug response, such as the Connectivity Map, to identify possible therapeutic interventions to lessen disease severity. **Aim 3:** Perform differential epigenetic state and gene expression and differential regulatory network analysis to better translate results from mouse model studies to understand drivers of human disease and we will develop methods to use single-cell data to deconvolute bulk tissue RNA-Seq. **Core C) Clinical Biorepository Core: Aim 1:** Obtain detailed clinical metadata and linked biological samples from subjects with established COPD, IPF and appropriate controls. **Aim 2:** Recruit a new cohort of subjects who will have an established clinical diagnosis of COPD (n=30), IPF (n=30) or age matched-controls (n=30).
Overlap: None

COMPLETED SUPPORT

P01 HL108801 (Perella) 08/15/2011-06/30/2017 1.86 calendar months
NIH/NHLBI (NCE)
Carbon Monoxide: Novel Opportunities for Therapy, Project 1
Role: Project 1 Leader
Name and address of Contracting/Grants Officer: Andrea Harabin, Ph.D., Program Director, Division of Lung Diseases; National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952

Goals: To improve our understanding on how carbon monoxide mediates its' cytoprotection will assist in the proof of concept studies in humans to examine whether inhaled carbon monoxide can be a potential therapy in human sepsis and acute lung injury.
Specific aims: This translational PPG will enable us to accomplish three major goals in our ultimate quest to use a novel cytoprotective molecule, CO, in the treatment of a dreadful disease such as ALI: i) elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses
can provide potent cytoprotection ii) identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI Hi) provide critical proof-of- concept "first in ALI" studies to prepare us for a CO intervention trial in ALI at the next Cycle II of the translational PPG program. The impact of reaching these 3 major goals will be significant in the critical care illness and pulmonary community as we hope to unravel new diagnostic biomarkers and/or treatment(s) for ALI. We will attempt to reach our goals by the addressing the following projects and cores: Projects: 1. Cytoprotection by Carbon Monoxide in Sepsis and Lung Injury 2. Carbon Monoxide and Mitochondrial Quality Control in Sepsis-induced Lung Injury 3. Mesenchymal Stromal Cell Conditioning by Carbon Monoxide 4. Carbon Monoxide and Specialized Pro-Resolving Mediators Cores: Core A: Administrative Core Core B: Clinical Studies Coordination Core Core C: Lipid Mediator Metabolomics Core D: Carbon Monoxide Delivery in Sepsis and Acute Lung Injury

Overlap

none

P01 HL105339 (Silverman) 08/17/2011-06/30/2017 0.6 calendar months
NIH/NHLBI $0 (NCE)

Functional Genetics of COPD

Role: Co-Investigator

Name and address of Contracting/Grants Officer: Lisa Postow, Ph.D., Program Director, National Heart, Lung, and Blood Institute, Two Rockledge Center, Suite 10162, MSC 7952, 6701 Rockledge Drive, Bethesda, Maryland 20892-7952

Goals: The overall goal of this PPG is to understand the genetic, genomic, and epigenetic determinants of variable susceptibility to develop COPD

Specific Aims: The three projects In this PPG focus on Genetics (Project 1, PI: Silverman); Gene Expression (Project 2, PI: Choi); and DNA Methylation (Project 3, PI: DeMeo). These projects will build on a substantial existing infrastructure of well-phenotyped study populations, experience in phenotypic characterization of COPD, and an extensive track record of both in vitro and in vivo functional assessment of COPD pathogenesis. There are likely multiple additional COPD susceptibility loci, which need to be discovered. Some of these genetic loci may be influenced primarily by epigenetic alterations (e.g. DNA methylation) instead of, or In addition to, heritable SNP variation. Moreover, the other gene members of the pathways related to these genetic determinants of COPD are unknown, and assessment of gene expression and DNA methylation can likely provide insight into these pathways. Thus, we have included Discovery of additional gene expression and epigenetic influences on COPD susceptibility as a central focus of this PPG. In addition, the actual genetic determinants within the GWAS loci have not been proven. Thus, we have included efforts to localize the key genes within those regions. Multiple approaches will be used to accomplish this goal. Including assessment of genetic association in a population of different genetic ancestry (African Americans from the COPDGene project), analysis of gene expression among genes within GWAS loci, assessment for epigenetic changes of genes within

GWAS loci, and assays of long-range gene regulation (e.g. chromosome conformation capture). In addition to Localization of the key determinants, Functional Validation will be required to confirm that specific genes are Involved in COPD pathogenesis and to understand their impact. We will employ both in vitro assessment within lung epithelial and monocyte cell lines (with validation in primary cell types) as well as in vivo assessment in murine models of underexpression (knockout) of the key genes and susceptible vs. resistant Inbred strains which are tested with long-term cigarette smoke exposure.

Overlap

None

R01 HL130826 (B. Ding) 05/01/2016-04/30/2021 0.6 calendar months

NIH/NHLBI

Endothelial cell-derived MMP14 in lung alveolar regeneration and fibrosis

Direct Cost: $288,368

Name and address of Contracting/Grants Officer: Qing "Sara" Lin, Ph.D., Program Director, Division of Lung Diseases; National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952

Goals: We have previously shown that in mice after removal of the left lung, blood vessels in the remaining right lungs express a molecule MMP14 to increase stem cell expansion and reduce scar formation, resulting in restoration of lung weight and function. Thus, we will study how blood vessel MMP14 modulates stem cell function and prevent scar formation in mouse models of lung injury. We also plan to selectively induce MMP14 expression in the blood vessel of damaged lungs to reinstate efficient lung regeneration. Our study will help to understand how supporting microenvironmental cells such as blood vessel regulate lung regeneration and scar formation. The outcome of our study can enable therapeutic strategy to regenerate a diseased lung without scar formation.

Specific Aims: To test this hypothesis, we will use mouse pneumonectomy and lung fibrosis model induced by repeated intratracheal injection of Bleomycin to 1) define how endothelial MMP14 processes HB-EGF and Cyr61 to regulate lung regeneration and fibrosis; 2) investigate FGFR1-dependent regulation of MMP14 function. Moreover, we also aim to combine PCEC-targeted gene transduction system and platelet infusion to direct MMP14 in the caveolae of PCECs to promote lung regeneration and prevent fibrosis. **Role:** Co-Investigator

Overlap

none

Participation ended Jan 2017.

R01 HL129875-01 (N. Dhillon) 09/01/2016-06/30/2020 0.6 calendar months

NIH/NHLBI

Impact of Opiate Abuse on HIV-Mediated Pulmonary Vascular Remodeling

Direct Cost: $335,944

Role: Co- Investigator

Name and address of Contracting/Grants Officer: Sandra Colombini Hatch, M.D., National Heart, Lung, and Blood Institute, Two Rockledge Center, Suite 10162, MSC 7952, 6701 Rockledge Drive, Bethesda, Maryland 20892-7952

Goals: The hypothesis of our study is that the combined exposure of pulmonary endothelial cells to HIV-protein(s) and morphine results in the induction of autophagy that leads to enhanced proliferation of endothelial cells and severe pulmonary vascular remodeling. We will evaluate the

effect of HIV- Tat and morphine on the oxidative stress mediated regulation of bulk autophagy in endothelial cells, delineate the role of autophagy/mitophagy in Tat and morphine mediated enhanced proliferation and focus on in-vivo investigation of PAH and autophagy in HIV-1 Tg rats with or without morphine exposure.
Specific Aims: In the first aim we will evaluate the effect of HIV- Tat and morphine on the oxidative stress mediated regulation of bulk autophagy in endothelial cells. In the second aim, we propose to delineate the role of autophagy/mitophagy in Tat and morphine mediated enhanced proliferation. Third aim will be focused on in-vivo investigation of PAH and autophagy in HIV-1 Tg rats with or without morphine exposure.
Overlap
none
Participation ended Jan 2017.

1 R01 HL112747-01 (Baron/Choi-Multi PI) 08/15/2012 – 04/30/2016 0.24 calendar months
NIH/NHLBI
The Inflammasome: A Novel Biomarker in ALI/ARDS
Direct Cost: $259,270
Dr. Choi relinquished his co-PI role in this grant in 2013, and Dr. Rebecca Baron assumed the PI role and contact PI of the grant. Dr. Choi requests 0.12 calendar months support during this transition period.
Role: Co-Investigator
Name and address of Contracting/Grants Officer: Lora Reineck, M.D., M.S., Medical Officer, National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: We therefore hypothesize that activation of the inflammasome plays a critical role in the development of infection-related ALI/ARDS and that statin administration may increase inflammasome-related downstream cytokines during lung injury.
Specific Aims: Specific Aim 1: To determine gene expression and protein levels of the inflammasome during infection-related ALI/ARDS using prospectively collected blood (n=100) and banked plasma samples (n=600) from placebo- and statin-treated SAILS subjects. Gene expression and protein levels of the inflammasome will be correlated with 60-day mortality and additional SAILS trial secondary outcomes. We hypothesize that circulating inflammasome levels will serve as a biomarker of severity and mortality of infection-related ALI/ARDS and that inflammasome levels in statin-treated subjects will correlate with clinical outcomes. Specific Aim 2: To determine the cellular localization of expression of the inflammasome complex and role of inflammasome activation on cellular responses and function, using primary neutrophils and monocytes isolated from prospectively enrolled placebo- and statin-treated SAILS subjects (n=100), as well as primary cells isolated from control ICU subjects (n=100).
Overlap
none

U01 HL105371 (Rosas) 09/24/2010-06/30/2015 0.3 calendar months
NIH/NHLBI
Phase II Trial of inhaled CO for the treatment of idiopathic pulmonary fibrosis
Direct Cost: $1,997,979
Role: Co-Investigator

Dr. Choi relinquished his current role of PI of this UO grant to Dr. Ivan Rosas in 2013. Dr. Choi will continue to participate in this project, and requested 0.30 calendar months during the transition.
Name and address of Contracting/Grants Officer: Jerry Eu, M.D., Division of Lung Diseases, NHLBI, National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: Our goal is to study the use of low-dose inhaled CO as a therapeutic agent to treat IPF in humans.
Specific aims: Specific Aim #1: To investigate whether, in IPF patients, 3 months of therapy with low dose inhaled CO results in a relative decrease in peripheral blood levels of MMP7 and stability in secondary indicators of disease progression. Specific Aim #2: To investigate the potential role of an IPF specific peripheral blood mononuclear gene expression signature to predict rates of disease progression and determine responsiveness to inhaled CO.
Overlap
none

MARY E. CHOI, MD – OTHER SUPPORT

ACTIVE GRANTS

W81XWH1810667 (A. Choi) 09/15/2018 – 09/14/2022 1.2 calendar months
Department of Defense
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Role: Co-Investigator
Direct Costs: $2,446,383
Name and address of Contracting/Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Goals: The major goal of this phase II study is to evaluate safety, tolerability, and efficacy of inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS

R01HL055330 (A. Choi/M. Choi) 04/01/2018 – 03/31/2022 2.28 calendar months
NIH/NHLBI
Inflammasomes: Regulation and Function in Acute Lung Injury
Role: Co-PI
Direct Costs: $299,995
Name and address of Contracting/Grants Officer: Lora A. Reineck, MD, Lung Biology & Disease Program, National Health Lung and Blood Institute; RKL2 BG RM 10171, 6701 Rockledge Dr, Bethesda, MD 20817
Goals: The overall goal is to understand the role of receptor-interacting protein-3 kinase (RIPK3)-dependent necroptosis pathway and inflammation in the pathogenesis of experimental acute lung injury (ALI) and in human disease such as ARDS. The project examines how mechanical injury or infection causes dysregulated fatty acid (FA) metabolism resulting in activation of RIPK3-dependent signaling and necroptosis, and that disruption of FA metabolism promotes macrophage inflammasome activation and pro-inflammatory cytokines production, which contributes to the development of ALI. We also determine whether necroptosis-related proteins and FA are associated with morbidity and mortality in patients with critical illness, including ARDS.
Specific Aims: Aim 1: To determine the regulation and function of RIPK3-dependent necroptosis in ALI. **Aim 2:** To determine the mechanisms by which necroptosis mediates NOX4-dependent NLRP3 inflammasome activation in ALI. **Aim 3:** To determine the clinical relevance of necroptosis and FA metabolism in the critically ill patients, including ARDS.
Overlap
None

R01DK113088 (L. Gudas) 12/04/2017 - 11/30/2021 0.54 calendar months
NIH/NIDDK
Gene Nutrient Interactions in Kidney Function
Role: Collaborator
Direct Costs: $270,000

Name and address of Contracting/Grants Officer: Krystyna E. Rys-Sikora, PhD, Program Director, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive Kidney Diseases; 9000 Rockville Pike, Bethesda, MD 20892
Goals: We propose to test the hypothesis that renal lipid accumulation is a key contributor to dysfunction in both the glomerular and tubular compartments of the kidney, and that this excess renal lipid accumulation and renal dysfunction can be reversed through the use of an agonist for the retinoic acid receptor β2 (RARβ2), a member of the nuclear receptor protein family of transcription factors.
Specific Aims: Using both a high fat diet (HFD)-induced model and *db/db* murine model of obesity-associated chronic kidney disease (CKD), we will test our hypothesis by the following specific aims: **Aim 1:** we will test (in preclinical drug efficacy studies) three selective RARβ2 agonists (AC261066, AC55649, and CD2314) to determine if these synthetic retinoids can (a) decrease the lipid deposition in the kidneys and (b) improve or stabilize kidney function in obesity-induced CKD. **Aim 2:** we will examine the molecular mechanism(s) by which RARβ2 agonists reduce lipid accumulation and renal inflammation using both mouse models. We will also test whether the RARβ2 agonists are acting via RARβ2 expressed in particular types of cells in the kidney through the use of renal cell type specific RARβ knockout mice. **Aim 3:** to understand the mechanism of action of RARβ2 agonists, we will determine whether RARβ agonists act directly on podocytes, mesangial cells, and proximal tubule cells via the RARβ2 receptor to modulate metabolism, proliferation, and/or differentiation through the use of cell culture models.
Overlap
None

R01HL133801 (M. Choi/A. Choi) 08/01/2017-07/31/2021 3.0 calendar months
NIH/NHLBI
Novel role of RIPK3-dependent necroptosis pathway in lung and kidney fibrosis
Role: Co-PI (Contact)
Direct Costs: $308,797
Name and address of Contracting/Grants Officer: Matt Craig, PhD, Program Director, Lung Transplantation Program, National Heart, Lung, and Blood Institute; Building 31, 31 Center Drive, Bethesda, MD 20892
Goals: The goal of this project is to understand the role of receptor-interacting protein-3 kinase (RIPK3) and its signaling target the mixed lineage kinase domain-like protein (MLKL) in the pathogenesis of organ fibrosis. We explore RIPK3 as a novel mediator of organ fibrosis with differential organ or tissue-specific effects through MLKL-independent and MLKL–dependent pathways in experimental models of kidney and lung fibrosis using unilateral ureteral obstruction (UUO)-induced kidney fibrosis, and in bleomycin-induced pulmonary fibrosis. We also explore whether the endogenous gaseous molecule carbon monoxide (CO) confers protection against multi-organ fibrosis by targeting either RIPK3 and/or FA-dependent pathways. RIPK3 and/or FA-biosynthetic proteins potentially serve as diagnostic biomarkers in predicting the severity of organ fibrosis and the efficacy of CO therapy.
Specific Aims: Aim 1: To characterize the function of RIPK3 and MLKL in the pathogenesis of organ fibrosis; **Aim 2:** To determine the pathogenic contribution of RIPK3-regulated fatty acid (FA) synthesis in fibrotic organs; **Aim 3:** To determine the role of the RIPK3 and the FA synthesis pathways in the therapeutic effects of CO in experimental lung and kidney fibrosis, and in human fibrosis.
Overlap

None

R01HL132198 (A. Choi/M. Choi) 01/01/2017-12/31/2020 2.4 calendar months
NIH/NHLBI
Metabolic dysfunction regulates mitophagy-dependent necroptosis in COPD
Role: Co-PI
Direct Costs: $326,474
Name and address of Contracting/Grants Officer: Lisa Postow, PhD, Program Officer, Chronic Obstructive Pulmonary Disease (COPD)/Environment, National Heart, Lung, and Blood Institute; Building 31, 31 Center Drive, Bethesda, MD 20892
Goals: The major goal is to understand the mechanisms underlying the pathogenesis of chronic obstructive pulmonary disease (COPD) that is primarily associated with cigarette smoking (CS). The project examines how
CS exposure causes epithelial cell metabolic disruption, impaired fatty acid (FA) synthesis, and mitochondrial dysfunction, leading to activation of PINK1-dependent mitophagy using experimental models of COPD. Mitophagy induced by CS in turn drives a pro-pathogenic mechanism dependent on the activation of programmed epithelial cell death, in particular necroptosis. Activation of this mitophagy-dependent necroptosis pathway in response to metabolic and mitochondrial dysfunction may adversely affect airway function and emphysema outcomes during CS-induced COPD pathogenesis.
Specific Aims: Aim 1: To determine the mechanisms by which CS induces mitophagy in the lung. **Aim 2:** To determine the effect of impaired OXPHOS and FA synthesis on the regulation of mitochondrial dynamics and biogenesis and their impact on experimental COPD. **Aim 3:** To determine the regulation of cellular necroptosis by CS and its impact on lung functional impairment in experimental models of COPD.
Overlap
None

R01HL060234 (M. Choi/A. Choi) 03/14/2014-01/31/2020 (NCE) 1.38 calendar months
NIH/NHLBI
Heme Oxygenase-1/Carbon Monoxide in Lung Vascular Injury
Role: Co-PI (Contact)
Direct Costs: $299,779
Name and address of Contracting/Grants Officer: Lei Xiao, M.D., Ph.D., Program Director & Medical Officer, National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: The major goal of this project is to determine the role of autophagy in pulmonary hypertension (PH). The project explores how autophagy represents an adaptive stress response to protect against PH, and that CO prevents PH via regulating autophagy. We also explore whether autophagy regulated inflammasomes can potentially serve as diagnostic biomarker in predicting severity of PH.
Specific Aims: Aim 1: To determine the mechanism by which CO-induced autophagy functions to provide cytoprotection in experimental PH. **Aim 2**: To determine the mechanism by which CO dampens the inflammasome pathway in experimental PH. **Aim 3**: To determine whether CO inhibits inflammasome and its regulated cytokines in human PH.
Overlap
None

P01HL114501 (A. Choi) 09/06/2013-06/30/2020 (NCE) 0.12 calendar months
NIH/NHLBI
Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers
Role: Co-Investigator (Project 1)
Direct Costs: $234,935 (Project 1)
Name and address of Contracting/Grants Officer: Dr. Antonello Punturieri, Division of Lung Diseases; National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: In this program project we have integrated the expertise of investigators from COPD and IPF community, both basic and translational, to come together to better understand the pathogenesis of these chronic lung diseases, and hopefully identify new molecular targets in the treatment of these dreadful diseases in the future.
Specific Aims: (Project 1) Homeostatic Role of Autophagy in Lung Emphysema and Fibrosis: **Aim 1:** Determine whether divergent regulation of autophagy in fibrosis and emphysema is TGF-β1 dependent or independent. **Aim 2:** Determine whether autophagy mediates emphysematous and/or fibrotic responses via mTOR independent or dependent pathway. **Aim 3:** Determine the role of mitochondria derived reactive oxygen species (ROS) and mitophagy in the development of emphysema or pulmonary fibrosis;
Overlap
None

PENDING GRANTS

P01 HL114501 (A. Choi) 04/01/2020-03/31/2025 0.6 calendar months (Proj 1)
NIH/NHLBI
Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers
Role: Co-Investigator
Direct Costs: $212,924
Name and address of Contracting/Grants Officer: David Goff, MD, Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Building 31, 31 Center Drive, Bethesda, MD 201892
Goals: In this program project we have integrated the expertise of investigators from COPD and IPF community, both basic and translational, to come together to better understand the pathogenesis of these chronic lung diseases, and hopefully identify new molecular targets in the treatment of these dreadful diseases in the future.
Specific Aims: Aim 1: To determine the functional significance of PINK1-regulated RIPK3 signaling in fibrosis and emphysema. **Aim 2:** To determine the mechanism(s) by which mitochondrial and metabolic pathways regulate PINK1-RIPK3 signaling in CS induced fibrosis and emphysema. **Aim 3:** To evaluate whether circulating cf-mtDNA and RIPK3 are associated with severity and progression of ILD and COPD.
Overlap
None

R61/R33 (A. Choi/L. Fredenburgh) 07/01/20–06/30/24 0.6 calendar months years 2-4
NIH/NHLBI

A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Role: Co-Investigator
Direct Costs: $348,291
Name and address of Contracting/Grants Officer: Lora Reineck, MD, MS, Program Director, Acute Lung Injury/Critical Care Program, Lung Biology and Disease Branch, National Heart, Lung, and Blood Institute, Building 31, 31 Center Drive, Bethesda, MD 20892
Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap
The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

COMPLETED GRANTS

CTSC Pilot Award (O. Akchurin) 09/05/2017 – 06/30/2019 0.12 calendar months
Clinical & Translational Science Center Pilot Award, Weill Cornell Medicine
Iron metabolism and bone health in juvenile chronic kidney disease
Role: Primary Mentor
Direct Costs: $50,000
Name and address of Contracting/Grants Officer: Juan J. Cordero, MD, Protocol and Regulatory Manager, Weill Cornell Medicine, Gertrude and Louis Feil Family Research Building (RR Building) 407 East 61st Street, Room: 221 New York, NY 10065-8736
Goals: The goal is to understand how iron therapy in juvenile chronic kidney disease (jCKD) affects bone growth and bone quality.
Specific Aims: Aim 1: Identify mechanisms of exogenous iron impact on bone formation, bone mechanical behavior, and linear growth in jCKD mice. **Aim 2:** Determine the effects of iron excess on PCD in cortical bone and growth plates in jCKD mice. **Aim 3:** Identify clinical correlations between iron status and iron therapy on parameters of linear growth and on regulation of the growth hormone (GH) axis in children with CKD.
Overlap
None

R01DK057661 (M. Choi) 06/01/2000 – 05/31/2017 3.6 calendar months
NIH/NIDDK
TGF-beta Signaling in the Kidney
Role: Principal Investigator
Direct Costs: $217,500

Name and address of Contracting/Grants Officer: Dr. Deborah K. Hoshizaki, Division of Kidney, Urologic & Hematologic, National Institute of Diabetes and Digestive and Kidney Diseases, BG 2DEM RM 6143, 6707 Democracy Blvd, Bethesda, MD 20817
Goals: This proposal is focused on examining the mechanism and functional role of TGF-β1 signaling via TAK1 in renal cells, and the regulation of autophagy and its physiological functional role in an experimental model of renal fibrosis.
Specific Aims: **Aim 1**: To determine the mechanism and functional role of TGF-β1 signaling via TAK1 in renal cells Specific **Aim 2**: To determine the regulation and function of autophagy induced by TGF-β1 in renal cells. Specific **Aim 3**: To determine the in vivo physiological functional role of autophagy in an experimental model of renal fibrosis. We will employ state-of-the art approaches including a variety of dominant negative mutants of the signal transducing molecules, the MAPKs, focusing on the TAK1-MKK3 signaling axis, gene silencing by the use short interfering RNA (siRNA), and genetically altered mice, the null mice for the various TAK1, MKK3, Caveolin-1, and the autophagy genes, LC3 and Beclin 1.
Overlap
None

R21HL125044 (J. Laurence) 08/20/2014 – 06/30/2016 0.25 calendar months
NIH/NHLBI
Mechanisms of HIV/ART related cardiac fibrosis
Role: Co-Investigator
Direct Costs: $154,320
Name and address of Contracting/Grants Officer: Bishow B. Adhikari, Heart Failure & Arrhythmias Branch, National health Lung and Blood Institute, RKL2 BG RM 8186, 6701 Rockledge Dr, Bethesda, MD 20817
Goals: This project is focused on examining HIV/antiretroviral therapy (ART) and its relationship to cardiac fibrosis. The project explores how, in the HIV+ but ART naive, fibrosis is a consequence of proinflammatory cytokine linked induction of tissue factor, leading to thrombin generation, platelet activation with release of TGF-β1, and Smad and TAK1/MKK3/p38-mediated signaling, resulting in accelerated collagen synthesis. In addition, physiologic facilitators of collagen degradation, such as Beclin1, may be blocked by soluble HIV gene products. We utilize our ongoing model for platelet TGFβ1-driven cardiac fibrosis in mice and explore how a ritonavir (RTV)-mediated phenomenon amplifies TRAF6 associated TGF-β1 signaling and cardiac fibrosis might be targeted through a novel approach employing carbon monoxide (CO) or CO inducers. We also examine banked plasma, serum and PBMC samples from 100 HIV+ and 100 HIV- women followed longitudinally for two years, the former either treatment-naive or on RTV-based versus other ART. These data should support proposals to pursue additional translational studies related to HIV/ART and CVD in our lab, as well as suggest possible clinical trials to intervene in HIV-associated CVD.
Specific Aims: Aim 1: To define the role of TGF-β1 in HIV and HIV/ritonavir-linked cardiac fibrosis and explore mechanisms of action. **Aim 2:** To investigate the ability of carbon monoxide (CO) and CO inducers to mitigate HIV/ritonavir-linked cardiac fibrosis in vitro, and in an animal model.
Overlap
None

5UL1 R000457-09 (O. Akchurin) 06/01/2016 – 05/31/2017 0.12 calendar months

Clinical & Translational Science Center Pilot Award, Weill Cornell Medicine
Growth delay and inflammation in juvenile chronic kidney disease
Role: Co-Investigator
Direct Costs: $50,000
Goals: The major goals are to study growth delay and inflammation in high-adenine diet induced CKD in juvenile (growing) mice.
Name and address of Contracting/Grants Officer: Juan J. Cordero, MD, Protocol and Regulatory Manager, Weill Cornell Medicine, Gertrude and Louis Feil Family Research Building (RR Building) 407 East 61st Street, Room: 221 New York, NY 10065-8736
Specific Aims: Aim 1: Optimize the high adenine diet regimen in juvenile male and female mice and define its effects on growth rate and inflammation. **Aim 2:** Investigate the role of TNF-alpha antagonist etanercept in uremic growth delay and inflammation using the adenine-induced CKD mouse model.
Overlap
None

R01HL079904 (M. Choi) 01/26/2014 – 12/31/2015 0.36 calendar months
NIH/NHLBI
Heme Oxygenase-1/Carbon Monoxide in Sepsis
Role: Principal Investigator
Direct Costs: $46,166
Name and address of Contracting/Grants Officer: Dr. Andrea L. Harabin, Lung Biology & Disease Program, National Health Lung and Blood Institute, RKL2 BG RM 10174, 6701 Rockledge Dr, Bethesda, MD 20817.
Goals: The goal of this project is to test the hypothesis that CO confers cyto- and tissue protection in endotoxemia/sepsis by preserving cellular homeostasis and promoting bacterial clearance through molecular regulation and activation of the autophagic pathway.
Specific Aims: Aim 1: To determine the regulation and function of CO-induced autophagy in mediating the cytoprotective effects of CO in sepsis **Aim 2:** To determine the mechanism by which CO-induced autophagic pathway mediates cytoprotection in experimental sepsis **Aim 3:** To perform proof-of-concept studies for biomarker detection and therapeutic efficacy to assist in the planning of Phase 1/Phase IIa trial for therapeutic efficacy of CO in human sepsis.
Overlap
None

MARIA PLATAKI, MD, PhD – OTHER SUPPORT
ACTIVE GRANTS

W81XWH1810667 (A. Choi) 09/15/2018 – 09/14/2022 6 calendar months
Department of Defense
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Role: Co-Investigator
Direct Costs: $2,446,383
Name and address of Contracting/Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Goals: The major goal of this phase II study is to evaluate safety, tolerability, and efficacy of inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS.

Department of Medicine Pre-Career Award 07/01/17- 06/30/20 3.48 calendar months
Weill Cornell Medicine Department of Medicine
Effects of diet-induced obesity on Ventilator Induced Lung Injury
Role: PI
Direct Costs: $100,000
Name and address of Contracting/Grants Officer: Kristen Brady Phone: 212-746-9163 Email: krb2016@med.cornell.edu
Goals: This award supports the PI in transitioning towards a successful career as an independent researcher.
Specific Aims: Aim 1: Determine the impact of high fat diet (HFD)-induced obesity on susceptibility to ventilator-induced lung injury (VILI) in mice. Aim 2: Investigate the role of mTORC1 and autophagy in the response of the lung to mechanical ventilation in HFD-fed mice.
Overlap: None

R01HL055330 (A. Choi/M. Choi) 04/01/2018 – 03/31/2022 0.78 calendar months
NIH/NHLBI
Inflammasomes: Regulation and Function in Acute Lung Injury
Role: Co-Investigator
Direct Costs: $299,995
Name and address of Contracting/Grants Officer: Lora A. Reineck, MD, Lung Biology & Disease Program, National Health Lung and Blood Institute; RKL2 BG RM 10171, 6701 Rockledge Dr, Bethesda, MD 20817
Goals: The overall goal is to understand the role of receptor-interacting protein-3 kinase (RIPK3)-dependent necroptosis pathway and inflammation in the pathogenesis of experimental acute lung injury (ALI) and in human disease such as ARDS. The project examines how mechanical injury or infection causes dysregulated fatty acid (FA) metabolism resulting in activation of RIPK3-dependent signaling and necroptosis, and that disruption of FA metabolism promotes macrophage inflammasome activation and pro-inflammatory cytokines production, which contributes to the development of ALI. We also determine whether necroptosis-related proteins and FA are associated with morbidity and mortality in patients with critical illness, including ARDS.
Specific Aims: Aim 1: To determine the regulation and function of RIPK3-dependent necroptosis in ALI. **Aim 2:** To determine the mechanisms by which necroptosis mediates NOX4-dependent

NLRP3 inflammasome activation in ALI. **Aim 3:** To determine the clinical relevance of necroptosis and FA metabolism in the critically ill patients, including ARDS.

Overlap

None

R01HL060234 (M. Choi/A. Choi) 03/14/2014-01/31/2020 (NCE) .118 calendar months

NIH/NHLBI

Heme Oxygenase-1/Carbon Monoxide in Lung Vascular Injury

Role: Co-Investigator

Direct Costs: $299,779

Name and address of Contracting/Grants Officer: Lei Xiao, M.D., Ph.D., Program Director & Medical Officer, National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952

Goals: The major goal of this project is to determine the role of autophagy in pulmonary hypertension (PH). The project explores how autophagy represents an adaptive stress response to protect against PH, and that CO prevents PH via regulating autophagy. We also explore whether autophagy regulated inflammasomes can potentially serve as diagnostic biomarker in predicting severity of PH.

Specific Aims: Aim 1: To determine the mechanism by which CO-induced autophagy functions to provide cytoprotection in experimental PH. **Aim 2**: To determine the mechanism by which CO dampens the inflammasome pathway in experimental PH. **Aim 3**: To determine whether CO inhibits inflammasome and its regulated cytokines in human PH.

Overlap

None

PENDING GRANTS

R61/R33 (A. Choi/ L. Fredenburgh) 07/01/2020 - 06/30/2024 0.36 calendar months yr1 1.2 calendar months yrs2-4

A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS

Role: Co-Investigator

Direct Costs: $348,291

Name and address of Contracting/Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.

Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.

Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

COMPLETED GRANTS

None

PREVIOUS/CURRENT/PENDING SUPPORT:

WINCHELL, ROBERT

PREVIOUS
None

CURRENT

W81XWH1810667 (A. Choi) 09/15/2018 – 09/14/2022 0.24 calendar months
Department of Defense
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Role: Co-Investigator
Direct Costs: $2,446,383
Name and address of Contracting/Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Goals: The major goal of this phase II study is to evaluate safety, tolerability, and efficacy of inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS

PENDING
None

OVERLAP
None

PREVIOUS/CURRENT/PENDING SUPPORT:

FREDENBURGH, LAURA

PREVIOUS:
Title: Carbon Monoxide: Novel Opportunities for Therapy (5P01HL108801-05)
Effort: 2.4 Calendar Months (Core D Co-Director; Project 1 Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Harabin, Andrea L. (andrea.harabin@nih.gov)
Performance Period: 08/15/11 – 06/30/17 (No Cost Extension)
Funding Amount: $224,641 (Core B) direct costs per year (No Cost Extension)
Project Goals: The major goal of this study is to investigate carbon monoxide as a novel therapy for sepsis and ARDS.
Specific Aims: The specific aims of this project are 1) to elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection; 2) to identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI; and 3) to provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI in Cycle II of the translational PPG program.
Overlap: There is no overlap.

Title: The Inflammasome: A Novel Biomarker in ALI/ARDS (5R01HL112747-04)
Effort: 1.2 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)
Performance Period: 05/15/12 – 04/30/17 (No Cost Extension)
Funding Amount: $259,270 direct costs per year (No Cost Extension)
Project Goals: The major goal of this study is to investigate the role of inflammasome activation in the development of infection-related ALI/ARDS and determine whether statins exacerbate lung injury and inflammation via activation of the inflammasome.
Specific Aims: The specific aims of this project are 1) to determine gene expression and protein levels of the inflammasome during infection-related ALI/ARDS using prospectively collected blood and banked plasma samples from placebo- and statin-treated SAILS subjects; and 2) to determine the cellular localization of expression of the inflammasome complex and role of inflammasome activation on cellular responses and function, using primary neutrophils and monocytes isolated from prospectively enrolled placebo- and statin-treated SAILS subjects, as well as primary cells isolated from control ICU subjects.
Overlap: There is no overlap.

Title: Arterial Stiffness in the Pathogenesis of Human Pulmonary Arterial Hypertension (5R03HL115106-02)
Effort: 1.2 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Xiao, Lei (lei.xiao@nih.gov)
Performance Period: 08/01/12 – 06/30/15 (No Cost Extension)
Funding Amount: $47,600 direct costs per year

Project Goals: The overall goal is to investigate arterial stiffness in human PAH using the resources of the Pulmonary Hypertension Breakthrough Initiative (PHBI).
Specific Aims: The specific aims of this project are 1) to investigate the magnitude and distribution of pathological increases in pulmonary arterial stiffness at the micron spatial scale in human PAH tissue; and 2) to elucidate the mechanisms by which the mechanical environment promotes pathologic remodeling behaviors in PASMC and PAEC derived from subjects with PAH.
Overlap: There is no overlap.

Title: Role of Cyclooxygenase-2-derived Prostanoids in Polymicrobial Sepsis (5K08GM083207-05)
Effort: 9.0 Calendar Months (PI)
Supporting Agency: NIH/NIGMS
Grants Officer: Somers, Scott D. (scott.somers@nih.gov)
Performance Period: 12/01/07 – 05/30/13 (No Cost Extension)
Funding Amount: $121,250 direct costs per year
Project Goals: The overall goal is to investigate the role of COX-2 in the pathogenesis of polymicrobial sepsis.
Specific Aims: The specific aims of this project are 1) to investigate the role of COX-2-derived prostanoids in a murine model of peritonitis-induced polymicrobial sepsis; 2) to elucidate the cell type(s) responsible for mediating the protective effects of COX-2 during peritonitis-induced polymicrobial sepsis; and 3) to determine the mechanisms by which COX-2 affords protection during sepsis.
Overlap: There is no overlap.

Title: Brigham Research Institute Fund to Sustain Research Excellence
Effort: 0 Calendar Months (PI)
Supporting Agency: Brigham Research Institute Fund, Brigham and Woman's Hospital
Grants Officer: Slavik, Jacqueline M. (jslavik@bwh.harvard.edu)
Performance Period: 07/01/17 – 12/31/17
Funding Amount: $50,000 direct costs per year
Project Goals: The overall goal of this award is to provide interim support to independent investigators who submitted a non-mentored NIH grant application that was reviewed but missed the funding payline.
Specific Aims: The specific aims are to investigate mechanotransduction and YAP/TAZ signaling in pulmonary arterial hypertension.
Overlap: There is no overlap.

Title: Mechanobiology of Vascular Remodeling in Pulmonary Arterial Hypertension (4R01HL114839-05)
Effort: 3.6 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Colombini-Hatch, Sandra (sandra.hatch@nih.gov)
Performance Period: 08/14/12 – 03/31/19 (NCE)
Funding Amount: $289,965 direct costs per year
Project Goals: The overall goal is to elucidate the role of matrix stiffness on pulmonary vascular remodeling and the pathobiology of pulmonary arterial hypertension.

Specific Aims: The specific aims of this project are 1) to investigate the temporal and spatial increases in PA stiffness and reversibility of mechanical changes during experimental PAH; 2) to determine whether increases in matrix stiffness trigger a "remodeling phenotype" in human PASMC and PAEC and investigate the role of COX-2 in orchestrating these stiffness-dependent cellular alterations; and 3) to elucidate how stiffness modulates gene expression and to identify key transcription factors involved in stiffness-dependent gene regulation in human PASMC and PAEC.
Overlap: There is no overlap.

Title: Defining the Complex Biology of the miR-130/301 Family in Pulmonary Hypertension (5R01HL124021-05)
Effort: 0.84 Calendar Month (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Xiao, Lei (lei.xiao@nih.gov)
Performance Period: 01/15/14 – 05/31/19
Funding Amount: $252,000 direct costs per year
Project Goals: The major goal of this study is to delineate the role of the miR-130/301 family in controlling pulmonary vascular proliferation and vasoconstriction and in promoting pulmonary hypertension.
Specific Aims: The specific aims of this project are 1) to determine the importance of PPARγ and endothelin-1 for control of pulmonary vasomotor tone by miR-130/301; 2) to determine the importance of PPARγ and TIMP2 for control of matrix deposition and pulmonary vascular stiffness by miR-130/301; and 3) to define the coordinated actions of the miR-130/301 family members on overall PH manifestation.
Overlap: There is no overlap.

Title: Aspergillus fumigatus Volatile Secondary Metabolite Dynamics for the Identification of Azole-resistant Aspergillosis (5R21AI130669-02)
Effort: 1.2 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NIAID
Grants Officer: Franceschi, Francois J. (francois.franceschi@nih.gov)
Performance Period: 03/01/17 – 02/28/19
Funding Amount: $150,000 direct costs per year
Project Goals: The major goal of this study is to test the hypothesis that the sesquiterpene secondary metabolite response to triazole antifungal therapy is distinct in azole-susceptible and azole-resistant *A. fumigatus* (ARAF), setting the groundwork for a novel, rapid breath assay that can distinguish patients with ARAF aspergillosis from azole-susceptible invasive aspergillosis, providing an *in vivo* indicator of imminent therapeutic failure, guiding selection of appropriate antifungal therapy, and reducing the extremely high morbidity and mortality associated with ARAF infections. Ultimately, we expect to delineate marked differences in the dynamics of volatile sesquiterpene secondary metabolite release in ARAF vs. azole- susceptible A. fumigatus, both in vitro and in vivo.
Specific Aims: The specific aims of this project are to test the hypothesis that the sesquiterpene secondary metabolite response to triazole antifungal therapy is distinct in azole-susceptible and azole-resistant A. fumigatus by (1) comparing the in vitro response of ARAF (including the most common cyp51A mutations TR34/L98H, TR46/Y121F/T289A, M220, and G54, and ARAF with phenotypic multi-azole resistance despite wild-type cyp51A) and azole-susceptible A. fumigatus

strains to azole antifungal therapy and (2) comparing the in vivo response of ARAF and azole-susceptible A. fumigatus to azole antifungal therapy in breath using a neutropenic murine IA model.
Overlap: There is no overlap.

CURRENT:
Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)
Effort: 2.4 Calendar Months (Site PI)
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)
Performance Period: 09/15/18 – 09/14/22
Funding Amount: $761,103 direct costs year 1
Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: There is no overlap.

Title: YAP/TAZ Regulation of TGF-β/BMP Signaling and Vascular Remodeling in PAH (AHA Grant-in-Aid)
Effort: 0.6 Calendar Months (PI)
Supporting Agency: American Heart Association
Grants Officer: McEnany, Rachel (Rachel.McEnany@heart.org)
Performance Period: 07/01/17 – 06/30/20 (NCE)
Funding Amount: $77,000 total costs per year
Project Goals: The major goal of this study is to investigate the role of the YAP/TAZ pathway in the regulation of TGF-β/BMP signaling in pulmonary arterial hypertension (PAH).
Specific Aims: The specific aims of this project are 1) to investigate the role of YAP and TAZ in regulation of TGF-β/BMP signaling and vascular remodeling in human PASMC and PAEC; and 2) to determine whether inactivation of YAP/TAZ by selective targeting of $G\alpha_s$-coupled GPCRs enhances BMP signaling, prevents vascular remodeling, and attenuates experimental pulmonary hypertension.
Overlap: There is no overlap.

Title: Mechanotransduction and YAP/TAZ Signaling in Pulmonary Arterial Hypertension (5R01HL137366-02)
Effort: 3.6 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Fessel, Joshua (josh.fessel@nih.gov)
Performance Period: 01/01/18 – 12/31/21
Funding Amount: $392,775 direct costs per year
Project Goals: The overall goal is to investigate mechanotransduction and the YAP/TAZ pathway in PAH.

Specific Aims: The specific aims of this project are 1) to investigate the role that YAP/TAZ play in regulating COX-2-dependent prostaglandin production and vascular responses to matrix stiffening in PAH; 2) to examine the mechanisms by which YAP/TAZ control TGF-β and BMP-dependent Smad signaling, suppress Id1 expression, and regulate cellular growth responses to BMP signaling in PAH; and 3) to determine whether inactivation of YAP/TAZ arrests pulmonary arterial stiffening, attenuates vascular remodeling, and prevents right heart dysfunction in experimental PH.
Overlap: There is no overlap.

Title: TSC2 Signaling in Pulmonary Arterial Hypertension (2R01HL113178-05)
Effort: 0.6 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Fessel, Joshua (josh.fessel@nih.gov)
Performance Period: 04/01/18 – 03/31/22
Funding Amount: $250,000 direct costs per year
Project Goals: The overall goal is to investigate TSC2 signaling in PAH.
Specific Aims: The specific aims of this project are 1) to critically test the activation status of TSC2 using de-identified lung tissue samples and cultured PAVSMC from idiopathic PAH patients and healthy donors; 2) to determine whether TSC2 deficiency in PAVSMC is induced by increased matrix stiffness and self-supported via Yap/Taz-dependent ECM remodeling; and 3) to evaluate whether epigenetic targeting of TSC2 by Sirt1 activator SRT2104 suppress proliferation and induce apoptosis in vitro in human PAH PAVSMC, reduces excessive ECM production and consequent hyper-proliferation of PAEC and PAAF, and reverses or attenuates experimental pulmonary vascular remodeling and PH in rodent SuHx and monocrotaline models.
Overlap: There is no overlap.

Title: Systems biology, endothelial regulation of fibrosis, and pulmonary vascular disease (1R01HL139613)
Effort: 0.12 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Xiao, Lei (xiaol@mail.nih.gov)
Performance Period: 01/01/18 – 12/31/21
Funding Amount: $250,000 direct costs per year
Project Goals: The overall goal is to investigate NEDD9 in regulating pulmonary vascular fibrosis and PAH in vitro and in vivo.
Specific Aims: The specific aims of this project are 1) to prove that NEDD9-Cys18 oxidative modification mediates fibrosis in HPAECs in vitro; 2) to demonstrate that endothelial exosomes mediate a fibrotic pathophenotype in HPASMCs; and 3) to establish that NEDD9 is a lynchpin molecule regulating pulmonary vascular fibrosis and PAH in vivo.
Overlap: There is no overlap.

Title: Rapid, Breath Volatile Metabolite-Based Diagnostic for Ventilator-Associated Pneumonia (VAP) (5R01AI138999-02)
Effort: 1.2 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NIAID
Grants Officer: Franceschi, Francois J. (francois.franceschi@nih.gov)
Performance Period: 06/01/18 – 05/31/23
Funding Amount: $746,656 direct costs per year

Project Goals: The overall goal is the development of a breath volatile metabolite platform for the rapid diagnosis of VAP, breath-based identification of its most common causative pathogens, S. aureus, P. aeruginosa, K. pneumoniae, E. coli, E. cloacae, and A. baumanii, and the rapid, real-time, in vivo detection of resistance to antibiotics commonly used for empiric VAP treatment, including methicillin resistance in S. aureus, carbapenem and cephalosporin resistance in Enterobacteriaceae, and resistance to multiple antibiotics in P. aeruginosa and A. baumanii.
Specific Aims: The specific aims of this project are 1) to expand upon *in vivo* breath signatures in murine VAP models to identify early differential breath volatile metabolite responses to antibiotic therapy in susceptible and non-susceptible organisms for each species-antibiotic combination and define robust breath volatile metabolite signatures that differentiate pneumonia; 2) to examine these species-specific volatile breath metabolite signatures in patients with suspected VAP at baseline and at early time points after starting empiric antibiotic therapy, and in ventilated patients with respiratory tract colonization with these organisms; and 3) to optimize GC-DMS peak-finding algorithms for the multiplex, automated identification of the breath volatile metabolite profile of VAP, specific identification of VAP, and within each species-antibiotic combination, the delineation of phenotypic susceptibility vs. non-susceptibility based on early changes in these metabolites with treatment.
Overlap: There is no overlap.

Title: Acute Lung Injury Group New England Program to Support PETAL Network Research (5U01HL122989-06)
Effort: 0 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)
Performance Period: 06/17/14 – 04/30/21
Funding Amount: $243,568 direct costs per year
Project Goals: The major goal of this project is to develop an innovative and multidisciplinary clinical research consortium in New England to facilitate research by the NHLBI PETAL Network.
Specific Aims: The specific aim of this project is to recruit patients for network ARDS studies and to assist in development and execution of clinical protocols for novel ARDS therapies. This consortium will work together to optimize research processes to screen, enroll, and retain a recruited population of critically ill patients.
Overlap: There is no overlap.

PENDING:
Title: Portable Life-Saving Variable Ventilation for ARDS (W81XWH-19-S-CCC1)
Effort: 1.2 Calendar Months (Co-Investigator)
Supporting Agency: Defense Medical Research and Development Program- Philips Research (Vicario)
Grants Officer: Challapali, Kiran (kiran.challapali@philips.com)
Performance Period: 01/01/20 – 06/30/22
Funding Amount: $808,332
Project Goals: The overall goal is to investigate a new strategy of mechanical ventilation based on variable ventilation (VV) to provide both a diagnostic tool and therapeutic benefits in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to optimize the VV parameters that will be tested in a Phase I RCT and develop computational models of human ARDS: (1a) optimize the

statistical distribution of pressure/volume fluctuations for maximum recruitment and surfactant release while minimizing inflammation; (1b) implement VV in the Trilogy ventilator and leverage features available in Trilogy (continuous respiratory mechanics measurements and plateau pressure monitoring) to enhance safety and automation of VV; (1c) develop a comprehensive mathematical model of ARDS including cardiopulmonary physiology and lung biomechanics and tune it with data from the RCT in Aim 2; and 2) to test the safety and feasibility (primary endpoint) as well as efficacy (secondary endpoint) of VV-based MV strategy in 30 patients with ARDS in a Phase 1 clinical trial: (2a) perform a 3-arm RCT with 2 different iterations of VV (VV1, VV2) vs. conventional MV; (2b) determine the effects of VV vs. conventional MV on safety and on efficacy endpoints including lung mechanics, arterial oxygenation, and surrogate markers of lung inflammation.
Overlap: There is no overlap.

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Effort: 3.6 Calendar Months in Year 1, 3.0 Calendar Months in Years 2-4 (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)
Performance Period: 07/01/20 – 06/39/24
Funding Amount: $348,291 direct costs year 1
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PREVIOUS/CURRENT/PENDING SUPPORT:

BARON, REBECCA

PREVIOUS SUPPORT

Title: Role of NOS2 in Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS) (5 R01 HL091957 05)
Effort: 2.4 Calendar Months (PI)
Supporting Agency: NIH/NIGMS
Grants Officer: Andrea Harabin, Ph.D. -- andrea.harabin@nih.gov
Performance Period: 04/01/2009 – 02/01/2014 (NCE to 2/1/2015)
Funding Amount: $250,000
Project Goals: To characterize the role of NOS2 in ARDS.
Specific Aims: (1) To determine the role of NOS2 in a murine model of sepsis-induced lung injury that mirrors human ARDS; (2) To examine the direct effect of NOS2 expression in the lung epithelial cell on surfactant expression and function during acute lung injury; and (3) To explore the role of NOS2-derived NO on regulation of human surfactant protein-B expression.
Overlap: None

Title: Continuous Monitoring and Separation of Blood for Mitigation of Sepsis (USAMRMC Protocol No. SSC-5901-00)
Effort: 0.84 Calendar Months (Co-Investigator)
Supporting Agency: DARPA
Grants Officer: Timothy Broderick, M.D.
Performance Period: 10/01/2011 – 03/31/2015
Funding Amount: $197,405 (subcontract)
Project Goals: To develop a blood separation device for sepsis treatment.
Specific Aims: The major goals of this project are to develop a comprehensive separation technology for diverse potential targets, ranging from soluble factors to activated neutrophils and platelet aggregates. These novel systems will be tested on preclinical animal models and ultimately on human samples obtained from critically ill septic patients.
Overlap: None

Title: The inflammasome: A novel biomarker in ALI/ARDS (5 R01 HL112747 04)
Effort: 2.4 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov
Performance Period: 05/15/2012 – 04/30/2017 (NCE)
Funding Amount: $259,270
Project Goals: To determine the role of the inflammasome in mediating the effects of administered statins on ARDS.
Specific Aims: (1) To determine gene expression and protein levels of the inflammasome during infection-related ALI/ARDS using prospectively collected blood and banked plasma samples from placebo and statin-treated subjects from the SAILS (Statins for Acutely Injured Lungs from Sepsis) study. (2) To determine the cellular localization of expression of the inflammasome complex and role of inflammasome activation on cellular responses and function, using primary neutrophils and

monocytes isolated from prospectively enrolled placebo- and statin-treated SAILS subjects, as well as primary cells isolated from control intensive care unit (ICU) subjects.
Overlap: None

Title: Translational PPG – Carbon Monoxide: Novel Opportunities for Therapy (5 P01 HL108801 05), Clinical Studies Coordination Core
Effort: 1.2 Calendar Months (Core Co-Director)
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov
Performance Period: 08/15/2011 – 06/30/2017 (NCE)
Funding Amount: $224,641
Project Goals: To serve as the Clinical Studies Coordination Core for the translational PPG whose major goal is to translate the findings of cytoprotective properties of carbon monoxide that have been observed in preclinical animal models, to human disease, including a "first in acute lung injury" Phase I carbon monoxide safety trial.
Specific Aims: (1) To identify patients with the systemic inflammatory response syndrome (SIRS), sepsis, and sepsis-induced acute lung injury (ALI); to collect and store plasma, RNA, and primary cells from these patients in a clinical biorepository; as well as to provide biostatistical support for Projects 1-4 for the analysis and interpretation of studies performed using these specimens. (2) To serve as the data coordinating center (DCC) for the Phase 1 first-in-Acute Lung Injury safety study for inhaled CO in sepsis-induced ALI in Project 1 and the proof-of-concept study with collection of muscle biopsies after inhaled CO in Project 2 in the translational PPG. Collection of samples as in Aim 1 will be undertaken pre- and post-CO exposure for distribution to the investigators in Projects 1-4 of the translational PPG. This core will support studies in all projects of the translational PPG.
Overlap: None

Title: Micro-RNAs in Acute Lung Injury (5R01GM115605)
Effort: 2.40 Calendar Months (PI [Multiple PI with Dr. Mark Feinberg])
Supporting Agency: NIH/NIGMS
Grants Officer: Sarah Dunsmore, Ph.D. -- dunsmores@nigms.nih.gov
Performance Period: 08/15/2015 – 05/31/2019
Funding Amount: $297,198
Project Goals: To investigate the role of miR-181b and downstream targets in regulating lung injury.
Specific Aims: (1) To explore the proximal mechanisms governing miR-181b expression in endothelial cells during sepsis; (2) To explore the mechanisms by which miR-181b regulates NF-kB and AKT/eNOS signaling and endothelial cell dysfunction induced by human plasma of septic subjects, and (3) examine the effect of altered miR-181b expression in experimental models of sepsis and sepsis-induced lung injury in mice.
Overlap: None

ACTIVE GRANTS
Title: The Acute Lung Injury Group New England Program to Support PETAL Network Research (5U01 HL122989)
Effort: 0.36 Calendar Months (Co-PI of the Brigham and Women's Hospital subsite)
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov

Performance Period: 6/17/2014 – 4/30/2021
Funding Amount: $241,462 (sub)
Project Goals: To evaluate new therapies for ARDS.
Specific Aims: The major goal of this proposal is to recruit patients for network ARDS studies and to assist in development and execution of clinical protocols for novel ARDS therapies.
Overlap: None

Title: Monitoring peripheral blood leukocyte and immune responses in health and disease (5U24AI18656)
Effort: 0.60 Calendar Months (Co-Investigator)
Supporting Agency: DOD
Grants Officer: Kataryzyna Bourcier, PhD -- katarzyna.bourcier@nih.gov
Performance Period: 06/23/2015 – 5/31/2020
Funding Amount: $289,676
Project Goals: To develop novel bedside diagnostics for sepsis.
Specific Aims: (1) To design microliter scan preparatory inertial microfluidic separation of leukocytes in peripheral blood and (2) To determine microliter scale assays of systemic and cell-based immune function.
Overlap: None

Title: PET/CT-Guided Personalized Mechanical Ventilation to Minimize Ventilator-Induced Lung Injury (5R01HL121228)
Effort: 0.96 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov
Performance Period: 01/01/2014 – 04/30/2024
Funding Amount: $478,897
Project Goals: To determine early biomarkers of lung injury.
Specific Aims: (1) To assess the effects of regional tidal volumetric strain on local pulmonary FDG kinetics, tissue neutrophilic inflammation, and neutrophil gene expression; (2) To ascertain the dependence of regional parenchymal damage, neutrophilic inflammation, and lung dysfunction at 24h of lung injury on earlier local cellular metabolic activity quantified with FDG-PET; and (3) Within the first 48h of mechanical ventilation in septic patients, to establish the relationship between pulmonary neutrophilic inflammation and both regional lung strain and the ensuing degree of lung dysfunction.
Overlap: None

Title: Regulation of neutrophil function by mesenchymal stromal cells during sepsis (5R01GM118456)
Effort: 0.48 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NIGMS
Grants Officer: Sarah Dunsmore, Ph.D. -- dunsmores@nigms.nih.gov
Performance Period: 05/10/2016 – 02/29/2020
Funding Amount: $192,500
Project Goals: To investigate the role of neutrophils in mediating the protective effects of mesenchymal stromal cells in sepsis.

Specific Aims: (1) To investigate the importance of SDF-1 for the therapeutic effects of MSCs in an experimental mouse model of sepsis, using cecal ligation and puncture (CLP); (2) To explore the interaction between MSCs and neutrophils during experimental sepsis in mice, and elucidate the role of MSC-derived SDF-1 to improve neutrophil function; and (3) To determine whether MSCs can reduce neutrophil dysfunction in cells harvested from patients with sepsis, and elucidate the role of SDF-1 in this MSC response.
Overlap: None

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)
Effort: 3.0 Calendar Months (Co-Investigator, Co-Director of DCC)
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Sandy Snyder -- sandy.j.snyder.ctr@mail.mil
Performance Period: 09/15/2018 – 09/14/2022
Funding Amount: $761,103 direct costs year 1
Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: None

Title: Therapeutic modulation of zinc for lung injury and mechanobiology (1R01HL142093)
Effort: 2.03 Calendar Months (Co-PI with Dr. Daniel Tschumperlin)
Supporting Agency: NIH/NHLBI/NIGMS
Grants Officer: Neil Aggarwal, M.D. -- neil.aggarwal@.nih.gov
Performance Period: 04/01/2019 – 03/31/2023
Funding Amount: $573,248
Project Goals: To investigate the role of zinc in mitigating stretch-induced lung injury and ARDS.
Specific Aims: (1) To determine the impact of zinc repletion on the response to cell stretch, in vitro; (2) To determine the effect of chemical rescue of zinc deficiency in response to cell stretch in murine ventilator-induced lung injury (VILI); and (3) To determine the incidence and impact of zinc deficiency in human ARDS.
Overlap: None

Title: Biomarkers of Interstitial Ling Abnormalities Predict Poor Outcomes in ARDS (R21HL145246)
Effort: 0.6 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: John Hrivnak -- john.hrivnak@nih.gov
Performance Period: 09/20/2019 – 08/31/2021
Funding Amount: $96,520
Project Goals: The major goals of this proposal are: Aim 1: To identify the frequency of pre-existing ILA in ARDSnet patients and to determine if ILA defines an ARDS subpopulation with an increased rate of mortality; Aim 2: To determine whether a plasma biomarker signature can be

identified that predicts worsened outcomes from ARDS in those patients with pre-existing ILA and in ARDS patients overall.
Overlap: None

PENDING GRANTS
Title: Portable Life-Saving Variable Ventilation for ARDS (W81XWH-19-S-CCC1)
Effort: 1.2 Calendar Months (PI)
Supporting Agency: Defense Medical Research and Development Program – Philips Research (Vicario)
Grants Officer: Kiran Challapali -- kiran.challapali@philips.com
Performance Period: 01/01/2020 – 06/30/2022
Funding Amount: $808,332
Project Goals: The overall goal is to investigate a new strategy of mechanical ventilation based on variable ventilation (VV) to provide both a diagnostic tool and therapeutic benefits in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to optimize the VV parameters that will be tested in a Phase I RCT and develop computational models of human ARDS: (1a) optimize the statistical distribution of pressure/volume fluctuations for maximum recruitment and surfactant release while minimizing inflammation; (1b) implement VV in the Trilogy ventilator and leverage features available in Trilogy (continuous respiratory mechanics measurements and plateau pressure monitoring) to enhance safety and automation of VV; (1c) develop a comprehensive mathematical model of ARDS including cardiopulmonary physiology and lung biomechanics and tune it with data from the RCT in Aim 2; and 2) to test the safety and feasibility (primary endpoint) as well as efficacy (secondary endpoint) of VV-based MV strategy in 30 patients with ARDS in a Phase 1 clinical trial: (2a) perform a 3-arm RCT with 2 different iterations of VV (VV1, VV2) vs. conventional MV; (2b) determine the effects of VV vs. conventional MV on safety and on efficacy endpoints including lung mechanics, arterial oxygenation, and surrogate markers of lung inflammation.
Overlap: None

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Effort: 0.36 Calendar Months in Year 1, 1.2 Calendar Months in Years 2-4 (Co-Investigator, Co-Director of CCC)
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov
Performance Period: 07/01/2020 – 06/39/2024
Funding Amount: $348,291 direct costs year 1
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing

Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PREVIOUS/CURRENT/PENDING SUPPORT:

Perrella, Mark A.

PREVIOUS GRANTS (active within past 5 years)

1. "Cardiomyocyte Differentiation Regulates Cardiac Function"
   3.6 calendar months
   NIH/NHLBI – 5R01HL102897-05 (Perrella, PI)
   Grants Management Specialist: Kevin Reeves; 301-594-6285; reeveskm@mail.nih.gov
   12/2/2010 – 11/30/2015 (with a NCE)
   $250,000 (per year)
   Project Goals: The overall goal is to investigate the role of Speg and cardiomyocyte differentiation in the regulation of cardiac function.
   Specific Aims: The specific aims of the proposal are to 1) investigate the role of Speg in CPC fate, commitment to the cardiomyocyte lineage, and cardiomyocyte differentiation; 2) decipher the mechanisms responsible for the development of cardiac dysfunction in the absence of Speg; and 3) determine the importance of Speg during cardiac injury (pressure overload) in adult mice.
   Overlap: none

2. "Carbon Monoxide: Novel Opportunities for Therapy"
   3.6 calendar months
   NIH/NHLBI – 5P01HL108801-05 (Choi/Perrella, PI), Project 3 (Perrella, Project Leader)
   Grants Management Specialist: Charmaine Parsad; 301-451-0152; parsadrc@mail.nih.gov
   08/15/2011 – 6/30/2017 (NCE)
   $240,749 (Year 5)
   Project Goals: Each project will integrate basic aims to determine novel mechanism(s) by which CO mediates its cytoprotection with translational aims focused on proof-of-concept non-human primate and human studies. The synergism between the projects and cores will provide the groundwork to conduct a Phase II inhaled CO intervention trial in ALI during Cycle II of this translational P01 application.
   Specific Aims: The specific aims of Project 3 are to 1) investigate the biological response of MSC administration to mice after the onset of microbial sepsis; 2) condition MSCs with CO, a downstream product of the cytoprotective enzyme HO-1, and investigate their biological response in mice with sepsis; 3) decipher the mechanisms responsible for the enhanced response of MSCs, after exposure to CO, in murine sepsis; and 4) advance the understanding of the human immune response to MSC therapy in sepsis using "humanized" mice and *in vitro* analyses.
   Overlap: none

3. "Functional Genetics of COPD"
   0.6 calendar months
   NIH/NHLBI – 5P01HL105339-05 (Silverman, PI), Core C (Perrella, Co-director)
   Grants Management Specialist: Taryn Cobb; 301-435-0170; cobbt@mail.nih.gov
   08/17/2011 – 6/30/2016
   $220,602 (Year 5, Core C)
   Project Goals: Recent genetic studies have found areas of the human genome that influence the risk of developing chronic obstructive pulmonary disease (COPD) in cigarette smokers. The

overall goal of this project is to find the specific genes in these areas and begin to determine why these genes are responsible for COPD risk. This study will improve our understanding of COPD, and it is an important first step towards developing new treatments for COPD.
Specific Aims: The specific aims of Core C are to 1) provide expertise in modeling of COPD in mice, 2) development novel lines of mice for study, 3) tissue harvest, storage, cataloging, and distribution, 4) histopathology service, and 5) imaging and flow cytometry. The expertise and techniques of Core C will be provided to each of the projects.
Overlap: none

4. "The Functional Consequences of the 17q12 Asthma Susceptibility Locus"
   0.36 calendar months
   NIH/NHLBI – 5R01 HL117837-03 (Raby, PI)
   Program Official: Weiniu Gan; ganw2@nhlbi.nih.gov
   07/01/2015 – 06/30/2019
   $499,427 per year
   Project Goals: The overall goal of this proposal is to conclusively identify the gene that is responsible for genetic associations observed with asthma on chromosome 17q12 and to characterize its molecular, cellular, metabolic and phenotypic consequences.
   Specific Aims: In Specific Aim 1, we will study inducible transgenic mice generated in our lab that conditionally over express ORMDL3 or GSDMB in bronchial epithelium. In Specific Aim 2, we will experimentally assess (via in vitro knockdown and over expression studies) the independent cellular consequences of ORMDL3 and GSDMB expression in human bronchial epithelial cells derived from individuals homozygous for the risk and protective 17q12 haplotypes. In Specific Aim 3, we will study the relationship of 17q12 haplotype with sphingolipid metabolism.
   Overlap: none

ACTIVE GRANTS

1. "Regulation of Neutrophil Function by Mesenchymal Stromal Cells During Sepsis"
   2.74 calendar months
   NIH/NIGMS – 5R01 GM118456-04 (Perrella, PI)
   Grants Management Specialist: Anna Hahn; 301-594-5506, hahnann@mail.nih.gov
   05/10/2016 – 02/29/2020
   $192,500 (per year)
   Project Goals: The overall goal is to investigate the regulation of neutrophil function by mesenchymal stromal cells during sepsis.
   Specific Aims: The specific aims of the project are 1) to investigate the importance of SDF-1 for the therapeutic effects of MSCs in an experimental mouse model of sepsis, using cecal ligation and puncture (CLP)**;** 2) to explore the interaction between MSCs and neutrophils during experimental sepsis in mice, and elucidate the role of MSC-derived SDF-1 to improve neutrophil function; and 3) to determine whether MSCs can rescue human neutrophil dysfunction in cells harvested from patients with sepsis, and elucidate the role of SDF-1 in this MSC response.
   Overlap: none

2. "Therapy of acute radiation syndrome and its complications by mesenchymal stromal cells conditioned with Toll-like receptor 9 agonists"

2.4 calendar months
NIH/NIAID – 5U01 AI138318-02 (Lederer, PI; Perrella, co-PI)
Scientific Research Contact: Carmen Rios, PhD; Carmen.Rios@nih.gov
03/01/2018 – 02/28/2023
$350,000 per year
The goal of the project are: 1) to test the hypothesis that pre-conditioning MSCs by CpG-ODN stimulation will enhance their beneficial effects on anti-microbial immune function and hematopoietic system recovery after radiation exposure; 2) to determine the biological effects of CpG-ODN stimulation on MSCs phenotype and function; and 3) to interrogate mechanisms responsible for protective effects of CpG-MSCs on radiation injury and recovery.
Overlap: none

3. "Systems Biology of Airway Disease"
0.6 calendar months
NIH/NHLBI – 5 P01 HL132825-03 (Weiss, PI)
Grants Management Specialist: Suzanne White; whitesa@nhlbi.nih.gov
09/01/2016 – 07/31/2021
$1,514,753 per year, total for all projects and core
Functional Genomics Core (Perrella, Co-Investigator)
The overarching goal of the program project, "Systems Biology of Airway Disease", is to identify common molecular determinants and pathways for asthma and COPD. These determinants will be identified through the use of a diverse array of molecular data — DNA sequencing and genomewide SNP data (Project 1), RNA-sequencing and expression data (Project 2), methylation sequencing and miRNA sequencing data (Project 3). The Functional Genomics Core will explore the functional importance of these molecular determinants and pathways for the development of asthma and COPD.
Overlap: none

4. "A Phase 2 Study of Inhaled CO for the Treatment of ARDS"
1.2 calendar months
Department of Defense (DoD) - W81XWH1810667 (Choi, PI; Perrella, Co-Investigator)
Grants officer: Sandy Snyder; sandy.j.snyder.ctr@mail.mil
09/15/2018 – 09/14/2022
$761,103 direct costs year 1
Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: none

5. "Phase 2 Study of Safety, Tolerability, and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease"
1.2 calendar months

Investigator Initiated Clinical Trial, Genentech / Roche (Rosas, PI; Perrella, medical monitor)
$11,377,605 total cost
This investigator initiated industry sponsored international multicenter clinical study will test the safety tolerability and efficacy of oral Pirfenidone in patients affected with Rheumatoid Arthritis associated interstitial lung disease. Patients will be treated with Pirfenidone or Placebo for 52 weeks; efficacy will be determined by measuring changes over the study period. Exploratory endpoints will include imaging and molecular biomarkers.
Overlap: none

PENDING GRANTS

1. "Mesenchymal Stromal Cells, Autophagy, and the Host Response to Systemic Bacterial Infection"
   2.4 calendar months
   NIH/NIGMS – 1 R01 GM136804-01 (Perrella, PI)
   Grants Management Specialist: Anna Hahn, hahnann@mail.nih.gov
   04/01/2020 – 03/31/2025
   $250,000 per year
   The goals of the project are 1) to decipher the importance of the autophagy pathway, for enhanced MSC function during sepsis, after CO pre-conditioning of MSCs *ex vivo*; 2) to determine the role of extracellular vesicles (EVs) in the paracrine actions of MSCs pre-conditioned with CO, and investigate the importance of autophagy in this response; and 3) to determine whether *ex vivo* pre-conditioning of MSCs with CO improves the outcome of autophagy protein deficient mice during sepsis.
   Overlap: none

2. "A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS"
   1.2 calendar months in years 2-4 (Perrella, Co-Investigator)
   NIH/NHLBI
   Grants Officer: Lora Reineck, lora.reineck@nih.gov
   07/01/2020 – 06/39/2024
   $348,291 direct costs year 1
   Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
   Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
   Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PREVIOUS/CURRENT/PENDING SUPPORT:

HOU, PETER

PREVIOUS:

Title: Protocolized Care for Early Septic Shock (ProCESS) and ARRA Supplement
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH/NIGMS P50 GM076659 (Angus)
Grants Officer: Sarah Dunsmore (sarah.dunsmore@nih.gov)
Performance Period: 09/01/2007-08/31/2013
Funding Amount: $127,296 ($1,200 per subject enrolled, 99 subjects enrolled) and $56,919
Project Goals: The study objective is to improve the management of septic shock by exploring the clinical, biological, and economic aspects of alternative resuscitation strategies.
Specific Aims: (1) To compare the clinical efficacy of alternative resuscitation strategies for septic shock. (2) To better understand the mechanisms by which resuscitation strategies affect clinical outcomes. (3) To assess the costs and cost-effectiveness of the alternative resuscitation strategies.
Overlap: There is no overlap.

Title: Endothelial Cell Signaling and Microcirculation in Sepsis
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH/NHLBI R01 HL091757 (Shapiro)
Grants Officer: Cheryl McDonald (mcdonalc@mail.nih.gov)
Performance Period: 06/15/2008-05/31/2013
Funding Amount: $11,086 ($270 per subject enrolled, 42 subjects enrolled)
Project Goals: The overall goal of this project is to study the role of the endothelium in sepsis in a large, heterogeneous group of patients who are being enrolled in the ProCESS trial.
Specific Aims: (1) To study biomarkers of endothelial activation in sepsis. (2) To study microcirculatory flow in sepsis.
Overlap: There is no overlap.

Title: Emergency Department Best Practices to Reduce Healthcare Associated Infections
Effort: 0.3 calendar month (Co-Investigator)
Supporting Agency: NIH/AHRQ R18-HS020013-01 (Schuur)
Grants Officer: Daryl Gray (darryl.gray@ahrq.hhs.gov)
Performance Period: 09/30/2010-09/29/2013
Funding Amount: $23,086
Project Goals: The goals are to quantify the extent to which HAI prevention programs have been implemented in U.S. EDs, to conduct systematic qualitative analysis of EDs that have implemented programs, and to develop a cost-effective toolkit for dissemination to ED leaders.
Specific Aims: (1) To determine the proportion of U.S. EDs that have implemented proven, cost-effective intervention strategies in each of three areas that are critical to prevention of HAIs: central line associated bloodstream infections (CLABSI), catheter associated urinary tract infections (CAUTI), and hand hygiene (HH). (2) Investigate cultural and organizational barriers to successful implementation of HAI prevention practices. (3) To develop an implementation toolkit for these three HAI areas in the ED, and to pilot its dissemination.

Overlap: There is no overlap.

Title: LIPS-A: Lung Injury Prevention Study with Aspirin
Effort: 0.9 calendar month (Co-Investigator)
Supporting Agency: NIH/NHLBI U01 HL108712 (Gajic)
Grants Officer: Andrea Harabin (andrea.harabin@nih.gov)
Performance Period: 07/01/2011-06/30/2014
Funding Amount: $147,426 (25 subjects enrolled)
Project Goals: The goal of this project is to conduct an efficacy and safety trial of aspirin for prevention of acute lung injury in ED patients determined to be at high risk for subsequent development of acute lung injury.
Specific Aims: (1) Determine the relationship between aspirin-triggered 15-epi-lipoxin formation and acute lung injury prevention and severity. (2) Determine the relationship between aspirin-mediated inhibition of thromboxane and acute lung injury prevention and severity. (3) Determine the relationship between platelet-neutrophil aggregates in whole blood and aspirin-mediated protection for ALI.
Overlap: There is no overlap.

Title: Late Cardiovascular Consequences of Septic Shock and ARRA Supplement
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH/NIGMS R01 GM097471 (Yende)
Grants Officer: Sarah Dunsmore (sarah.dunsmore@nih.gov)
Performance Period: 06/01/2012-05/31/2017
Funding Amount: $14,100 ($600 per subject enrolled, 47 subjects enrolled) and $9,900
Project Goals: The objectives for this long-term follow-up study will be to examine patients who were enrolled in the ProCESS clinical study or who had a clinical diagnosis of sepsis for the effect of Protocolized resuscitation on the development of AKI, the recovery of kidney function, late cardiovascular events, quality of life, and long-term mortality.
Specific Aims: (1) To test the hypothesis that protocolized resuscitation prevents or lessens severity or duration of AKI. (2) To determine which pathophysiological derangements, in combination or individually, are associated with the development of AKI and CVD. (3) To determine whether biomarkers can predict AKI and recovery from AKI in the setting of sepsis.
Overlap: There is no overlap.

Title: Clinical performance of FebriDx in patients being evaluated for acute community acquired febrile respiratory infection
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: Rapid Pathogen Screening, Inc. Protocol 13-0830 (Shapiro)
Grants Officer: Jennifer Kasper (nursey05@gmail.com)
Performance Period: 02/07/2014-06/30/2016
Funding Amount: $30,400 ($800 per subject enrolled, 38 subjects enrolled)
Project Goals: The major goal of this project is to evaluate a new point of care rapid diagnostic test called FebriDx, a test that identifies an immune response to a viral and/or bacterial cause of a community acquired respiratory infection.
Specific Aims: (1) To determine the negative and positive agreement of the FebriDx test at identifying an immune response to viral and bacterial/co-infection related to an acute community acquired febrile respiratory infection as compared to expert clinical reviewers' evaluation and the

results of clinical standardized microbiologic, laboratory, and/or radiological testing. (2) Evaluation of MxA ELISA to determine the marker's specificity to confirm the presence of a viral infection.
Overlap: There is no overlap.

Title: Evaluation of Acute Respiratory Distress Syndrome in Patients Enrolled in the Protocolized Care for Early Septic Shock Trial (ProCESS-ARDS)
Effort: 0.12 calendar month (PI)
Supporting Agency: Eleanor and Miles Shore Fellowship Program for Scholars in Medicine, Harvard Medical School (Hou)
Grants Officer: Joshh Magee, Brigham and Women's Hospital, Department of Emergency Medicine (jmagee1@partners.org)
Performance Period: 07/01/2012-06/30/2016
Funding Amount: $35,000
Project Goals: The major goal of this project is to inform the feasibility of participation from other ProCESS sites in order to determine the overall incidence of Sepsis-induced ARDS in US academic teaching hospitals.
Specific Aims: (1) to determine the incidence of ARDS in patients presenting to the ED with septic shock enrolled in the ProCESS trial; (2) to design and apply a standard operating procedure for the retrospective evaluation of ARDS development in patients enrolled the ProCESS trial at two high enrolling study sites.
Overlap: There is no overlap.

Title: Rapid Administration of Carnitine in sEpsis (RACE) Trial
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH/NIGMS R01 GM103799 (Jones)
Grants Officer: Sarah Dunsmore (sarah.dunsmore@nih.gov)
Performance Period: 10/01/2014-05/31/2018 (5 subjects enrolled)
Funding Amount: $10,000 ($2,000 per subject enrolled, 5 subjects enrolled)
Project Goals: The major goal of this project is to conduct an efficacy and safety trial of L-carnitine as a novel adjunctive treatment for patients in septic shock.
Specific Aims: (1) To test if intravenous L-carnitine reduces cumulative organ failure in septic shock. (2) To test if L-carnitine improves blood flow in the sublingual microvasculature during septic shock.
Overlap: There is no overlap.

Title: A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: La Jolla Pharmaceutical Company, Inc. (Tidmarsh)
Grants Officer: Dan Yaeger (858-207-4264)
Performance Period: 03/30/2015-02/19/2017
Funding Amount: $33,483
Project Goals: The primary objective of this project is to compare the effect of LJPC-501 infusion on mean arterial pressure in patients with CRH.
Specific Aims: (1) To compare change in Sequential Organ Failure Assessment (SOFA) scores. (2) To establish the safety and tolerability of LJPC-501 and compare to placebo in patients with CRH.
Overlap: There is no overlap.

Title: LOw Tidal volume Universal Support: Feasibility of RecrUitment for Interventional Trial (LOTUS FRUIT)
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH HL123009 (Steingrub)
Grants Officer: Andrea Harabin (andrea.harabin@nih.gov)
Performance Period: 06/22/2016-04/30/2017
Funding Amount: $7,944 (53 subjects enrolled)
Project Goals: This study is an assessment of hospital mechanical ventilation practices.
Specific Aims: (1) To inform the design and plan for a pragmatic interventional cluster randomized control trial of low tidal volume ventilation in the emergency department and intensive care unit. (2) To determine the feasibility of data collection for patients with acute respiratory failure in a pragmatic trial.
Overlap: There is no overlap.

Title: LOw Tidal volume Universal Support: Feasibility of RecrUitment for Interventional Trial (LOTUS FRUIT) Protocol Study co-Chair
Effort: 0.24 calendar month
Supporting Agency: NIH U01HL123009, CCC for NHLBI Prevention and Early Treatment of Acute Lung Injury PETAL Network (MGH)
Grants Officer: Andrea Harabin (andrea.harabin@nih.gov)
Performance Period: 05/01/2016-04/30/2017
Funding Amount: $6,216
Project Goals: The overall project goal is to assess hospital mechanical ventilation practices.
Specific Aims: (1) To inform the design and plan for a pragmatic interventional cluster randomized control trial of low tidal volume ventilation in the emergency department and intensive care unit. (2) To determine the feasibility of data collection for patients with acute respiratory failure in a pragmatic trial.
Overlap: There is no overlap.

Title: Procalcitonin Antibiotic Consensus Trial (ProACT)
Effort: 0.12 calendar month(Co-Investigator)
Supporting Agency: NIH/NIGMS R01 GM101197 (Huang)
Grants Officer: Sarah Dunsmore (sarah.dunsmore@nih.gov)
Performance Period: 08/01/2014-07/31/2017
Funding Amount: $206,104 ($1,110 per subject enrolled, 205 subjects enrolled)
Project Goals: The study objective is to target emergency department (ED) patients with clinically diagnosed lower respiratory tract infection (LRTI) and test the effects of implementation of a procalcitonin antibiotic guideline for LRTI.
Specific Aims: (1) To determine the effect of implementation of a procalcitonin guideline on antibiotic exposure in clinically diagnosed LRTI. (2) To determine the effect of implementation of a procalcitonin guideline on a 30-day combined adverse outcome.
Overlap: There is no overlap.

Title: Reevaluation Of Systemic Early neuromuscular blockade (ROSE)
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH/NHLBI U01 HL123009 (Steingrub)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 11/16/2015-04/30/2018
Funding Amount: $73,557 ($7,910 per subject enrolled, 16 subjects enrolled)
Project Goals: The goal of this project is to assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate-severe ARDS in comparison to a control group with no routine early neuromuscular blockade.
Specific Aims: To assess if early neuromuscular blockade will improve mortality prior to discharge home before day 90, in patients with moderate-severe ARDS.
Overlap: There is no overlap.

Title: Effect of randomization to neuromuscular blockade on physical functional impairment and recovery in ARDS (PRIMROSE)
Effort: 1.2 calendar months (Co-Investigator)
Supporting Agency: NIH R01HL132232-02 (Hough)
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 8/16/2016-6/30/2019
Funding Amount: $154,886
Project Goals: The goals are to conduct a prospective longitudinal cohort study nested within the ROSE RCT, and extensively leveraging the ROSE RCT's patients screening, enrollment and follow-up infrastructure and to use stage-appropriate multi-modal assessments of neuromuscular function to identify the effect of randomization to NMB.
Specific Aims: To determine the effect of NMB (1) on the early development of ICU-acquired neuromuscular dysfunction, assessed primarily via nerve conduction study in the ICU; (2) on muscle function and strength at hospital discharge, assessed primarily using standardized handgrip dynamometry; and, (3) on physical recovery and healthcare utilization 6 and 12 months after the development of severe ARDS, assessed primarily using the Short Physical Performance Battery and the Medical Expenditure Panel Survey questionnaire.
Overlap: There is no overlap.

Title: Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH HL123009 (Steingrub)
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 12/01/2016-04/30/2019
Funding Amount: $236,146 ($3,326 per subject enrolled, 71 subjects enrolled)
Project Goals: To assess the efficacy and safety of early administration of vitamin D_3 (cholecalciferol) in reducing mortality and morbidity for vitamin D deficient patients at high risk for ARDS and mortality.
Specific Aims: To determine if early administration of vitamin D3 (cholecalciferol) will improve all-cause, all-location mortality to day 90 in vitamin D deficient patients at high risk for ARDS and mortality.
Overlap: There is no overlap.

Title: Reverse Engineering Host Resilience
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: Defense Advances Research Projects Agency (DARPA) – Presidents and Fellows of Harvard College (Harvard) – Beth Israel Deaconess Medical Center (BIDMC)

Grants Officer: Rachel Talentino (rachel_talentino@harvard.edu)
Performance Period: 03/03/2017-09/02/2018
Funding Amount: $42,635 (100 subjects enrolled)
Project Goals: To develop an assay that offers a rapid, simple, sensitive and specific method for diagnosing infections.
Specific Aims: The aims of this project are recruitment of patients with sepsis as well as non-infected control subjects for participation in the study, obtaining blood samples and delivering them to the Wyss Institute for analysis, and collecting and recording the key data elements that characterize the corresponding clinical phenotype and outcomes for each study subject
Overlap: There is no overlap.

Title: LJ501-EAP01 Expanded Access for LJPC-501
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: La Jolla Pharmaceutical Company, Inc. (Chawla)
Grants Officer: Dennis Mulroy (Dennis.Mulroy@ljpc.com)
Performance Period: 09/19/2017-02/14/2018
Funding Amount: $13,717
Project Goals: The goal of the study is to provide access to LJPC-501 for distributive shock patients who remain hypotensive despite receiving fluid and vasopressor therapy while the drug is in mass production.
Specific Aim: To continue the safety assessment of LJPC-501 after FDA approval.
Overlap: There is no overlap.

CURRENT:

Title: Acute Lung Injury Group New England (ALIGNE) Clinical Center Program to Support PETAL Network
Effort: 0.24 calendar month (Co-Investigator)
Supporting Agency: NIH/NHLBI U01 HL122989 (Steingrub)
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 06/17/2014-04/30/2021
Funding Amount: $175,404
Project Goals: Brigham and Women's Hospital is a satellite site of the ALIGNE clinical center. The Network will develop and conduct at least 3-5 randomized controlled clinical trials to prevent, treat, and/or improve the outcome of adult patients with, or at risk for, ALI or the acute respiratory distress syndrome (ARDS).
Specific Aims: Each CC will be expected to enroll 220 patients over 5.5 years.
Overlap: There is no overlap.

Title: PETAL Network: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS)
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: NIH HL123009 (Steingrub)
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 11/01/2017-04/30/2021
Funding Amount: $32,724 ($3,636 per subject enrolled, 9 subjects enrolled as of 10/7/2019)

Project Goals: The goal of the project is to assess the effect of the combination of vasopressor and fluid therapies in sepsis-induced hypotension on patient outcome.
Specific Aims: To determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) as compared to a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.
Overlap: There is no overlap.

Title: Ascorbic Acid, Hydrocortisone, and Thiamine in Sepsis and Septic Shock – A Randomized, Double-Blind, Placebo-Controlled Trial (ACTS)
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: Good Ventures – BIDMC (Donnino)
Grants Officer: Chris Somerville and Heather Youngs
Performance Period: 06/01/2018-05/31/2019
Funding Amount: $113,953 ($6,500 per subject enrolled, 15 subjects enrolled as of 10/7/2019)
Project Goals: The goal of this project is to assess the effect of a metabolic resuscitation bundle of therapies in septic shock on patient outcomes.
Specific Aims: This project aims to determine the impact of vitamin C, hydrocortisone, and vitamin B1 vs. placebo on organ injury and mortality in participants with sepsis and septic shock.
Overlap: There is no overlap.

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)
Effort: 0.24 calendar month (Co-Investigator)
Supporting Agency: Army Medical Research and Material Command (Choi)
Grants Officer: Sandy Snyder (sandy.j.snyder.ctr@mail.mil)
Performance Period: 09/15/2018-09/14/2022
Funding Amount: $761,103 direct costs year 1
Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1)to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: There is no overlap.

Title: DIStinguish Respiratory Underlying Pathogen associaTed host response in Acute Respiratory Infection: An Evaluation of FebriDx® POC Test (FebriDx® DISRUPT ARI Trial)
Effort: 0.12 calendar month (Co-Investigator)
Supporting Agency: Rapid Pathogen Screening, Inc. Protocol 13-0830 (Shapiro)
Grants Officer: Annie Bell (annie.bell@lumosdiagnostics.com)
Performance Period: 4/30/2019-10/30/2020
Funding Amount: $1,100 per subject enrolled (Subject enrollment to begin on 10/15/2019)
Project Goals: The major goal of this project is to evaluate a new point of care rapid diagnostic test called FebriDx®, a test that identifies an immune response to a viral and/or bacterial cause of a community acquired respiratory infection.

Specific Aims: The aim of this study is to determine performance characteristics of the FebriDx® test in predicting viral or bacterial infection etiology among febrile (observed or reported) patients presenting the emergency department, urgent care centers or primary care offices with suspected acute respiratory tract infection.
Overlap: There is no overlap.

PENDING:

Title: Portable Life-Saving Variable Ventilation for ARDS (W81XWH-19-S-CCC1)
Effort: 1.2 calendar months (Co-Investigator)
Supporting Agency: Defense Medical Research and Development Program – Philips Research (Vicario)
Grants Officer: Kiran Challapali (kiran.challapali@philips.com)
Performance Period: 01/1/2020-06/30/2022
Funding Amount: $808,332
Project Goals: The overall goal is to investigate a new strategy of mechanical ventilation based on variable ventilation (VV) to provide both a diagnostic tool and therapeutic benefits in patients with ARDS.
Specific Aims: The specific aims of this project are 1) Optimize the VV parameters that will be tested in a Phase I RCT and develop computational models of human ARDS: (1a) Optimize the statistical distribution of pressure/volume fluctuations for maximum recruitment and surfactant release while minimizing inflammation; (1b) Implement VV in the Trilogy ventilator and leverage features available in Trilogy (continuous respiratory mechanics measurements and plateau pressure monitoring) to enhance safety and automation of VV; (1c) Develop a comprehensive mathematical model of ARDS including cardiopulmonary physiology and lung biomechanics and tune it with data from the RCT in Aim 2; 2) Test the safety and feasibility (primary endpoint) as well as efficacy (secondary endpoint) of VV-based MV strategy in 30 patients with ARDS in a Phase 1 clinical trial: (2a) Perform a 3-arm RCT with 2 different iterations of VV (VV1, VV2) vs. conventional MV; (2b) Determine the effects of VV vs. conventional MV on safety and on efficacy endpoints including lung mechanics, arterial oxygenation, and surrogate markers of lung inflammation.
Overlap: There is no overlap.

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Effort: 0.24 calendar month in Years 2-4 (Co-Investigator)
Supporting Agency: NIH/NHLBI (Fredenburgh)
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 07/01/2020-06/39/2024
Funding Amount: $348,291 direct costs year 1
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to

achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PREVIOUS/CURRENT/PENDING SUPPORT:

EL-CHEMALY, SOUHEIL

PREVIOUS:
Title: Intracellular Actions of the Lymphangiogenic Growth Factor VEGF-D in Fibroblasts (K22HL092223)
Effort: 9 Calendar Months (PI)
Supporting Agency: NIH/ NHLBI
Grants Officer: Colombini-Hatch, Sandra (sandra.hatch@nih.gov)
Performance Period: 06/01/2011-06/01/2013
Funding Amount: $150,000 direct costs per year
Project Goals: The aim of this study is to study the nuclear localization and function of VEGF-D, the mechanisms of transport from cytoplasm to nucleus, and its role in the fibrotic process in IPF.
Specific Aims: Aim 1. To investigate the role of VEGF-D in transcriptional regulation in fibroblasts. **Aim 2.** To investigate the VEGF-D motif(s) required for its intracellular trafficking and interaction with RNA pol II. **Aim 3.** To investigate the role of VEGF-D as a key element of the fibro-proliferative process in idiopathic pulmonary fibrosis (IPF).
Overlap: There is no overlap.

Title: Effects of lymphangiogenesis stimulation on lung allograft rejection (R21HL119902)
Effort: 1.8 Calendar Months (PI)
Supporting Agency: NIH/ NHLBI
Grants Officer: Eu, Jerry P.C. (jerry.eu@nih.gov)
Performance Period: 08/01/2013-11/30/2015
Funding Amount: $150,465 direct costs per year
Project Goals: The goal of this study is to investigate the roles of the lymphatic circulation in the long term health of lung allograft, and to investigate the effect of treatment with VEGF-C C156S on lymphangiogenesis and graft function and to examine the role lymphatic vessel clearance of hyaluronan plays in allograft rejection.
Specific Aims: Aim 1. Will test the hypothesis that inducing lymphangiogenesis after established rejection will lead to decreased signs of graft rejection and improved lung function. **Aim 2.** Will test the hypothesis that the induction of lymphangiogenesis will result in enhanced HA clearance that will lead to improved lung allograft function.
Overlap: There is no overlap.

Title: Zebrafish xenotransplantation model to study Hermansky-Pudlak Syndrome pulmonary fibrosis
Effort: 1.2 Calendar Months (PI)
Supporting Agency: American Thoracic Society/American Lung Association
Grants Officer: Nebel, Erin Marie (emnebel@thoracic.org)
Performance Period: 01/15/2014-01/14/2016
Funding Amount: $40,000 direct costs per year
Project Goals: The goals of this proposal are to investigate phenotypic differences between the HPS lung fibroblast and the normal lung fibroblast and to establish zebrafish as a low cost model to study the pathogenesis of HPS pulmonary fibrosis.

Specific Aims: Aim 1. To investigate HPS-1 lung fibroblast ability to migrate and induce angiogenesis *in vitro*. **Aim 2.** To establish zebrafish as an *in vivo* model to study HPS pulmonary fibrosis lung fibroblasts. **Aim 3.** To study the expression of angiogeneic growth factors and other fibroblast derived proteins in lung tissue and in sera of subjects with HPS pulmonary fibrosis.
Overlap: There is no overlap.

Title: Critical roles for SYK in lymphangiogenesis in LAM (TS130031)
Effort: 1.2 Calendar Months (PI)
Supporting Agency: U.S. Army Medical Research Acquisition Activity
Grants Officer: Athansiou, Meropi (meropi.athanasiou.civ@mail.mil)
Performance Period: 09/01/2014-08/31/2016
Funding Amount: $50,000 direct costs per year
Project Goals: The goals of this study are to investigate mechanisms of dysregulated VEGF-D in LAM, particularly the role that inflammatory cells play in this process.
Specific Aims: Aim 1. To investigate the molecular pathogenesis of TSC2 deficiency in the induction of lymphangiogenesis *in vitro*. **Aim 2.** To determine the impact of pharmacological inhibition of SYK on lymphangiogenesis *in vivo* in a xenograft model. **Aim 3.** To study the expression of SYK and MCP-1 in LAM lung and peripheral blood.
Overlap: There is no overlap.

Title: Targeting Autophagy for the Treatment of TSC and LAM (W81XWH-12-1-0578)
Effort: 0 Calendar Months (Co-I)
Supporting Agency: U.S. Army Medical Research Acquisition Activity
Grants Officer: Athansiou, Meropi (meropi.athanasiou.civ@mail.mil)
Performance Period: 09/30/2012-09/29/2017 (NCE)
Funding Amount: $264,341 direct costs per year
Project Goals: The goals of this phase I clinical trial are 1) To investigate whether, in LAM patients, the combination of sirolimus and hydroxychloroquine is safe and well tolerated; 2) To investigate whether, in LAM patients, 6 months of combination therapy with sirolimus and hydroxychloroquine results in improvement of indicators of disease, and whether the gains are sustained after stopping therapy; and 3) To investigate the potential role of a LAM-specific peripheral blood signature to predict rates of disease progression and determine responsiveness to combination therapy.
Specific Aims: Aim 1. To investigate whether, in LAM patients, the combination of sirolimus and hydroxychloroquine is safe and well tolerated. **Aim 2.** To investigate whether, in LAM patients, 6 months of combination therapy with sirolimus and hydroxychloroquine results in improvement of indicators of disease, and whether the gains are sustained after stopping therapy. **Aim 3.** To investigate the potential role of a LAM-specific peripheral blood signature to predict rates of disease progression and determine responsiveness to combination therapy.
Overlap: There is no overlap.

Title: Rare Diseases Clinical Research Network/Rare Lung Diseases Consortium (5U54HL127672-04)
Effort: 0.1 Calendar Months (Co-I)
Supporting Agency: NIH/NHLBI/NCATS
Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)
Performance Period: 08/01/2015-07/31/2018

Funding Amount: $6,233,305 direct costs per year
Project Goals: This grant aims to study rare lung diseases, including Lymphangioleiomyomatosis (LAM), Pulmonary Alveolar Proteinosis (PAP), and Hermansky-Pudlak Syndrome (HPS), as well as other rare lung diseases. This consortium includes longitudinal and treatment studies, development of biomarkers and novel diagnostics, and outcomes measures, as well pilot project and training programs.
Specific Aims: The proposed Specific Aims include 1) establish a Consortium focused to Lymphangioleiomyomatosis (LAM), Pulmonary Alveolar Proteinosis (PAP), and Hermansky-Pudlak Syndrome (HPS), 2) conduct longitudinal and therapeutic clinical studies related to LAM, PAP, and HPS at abroad network of rare lung disease clinical centers established initially via LAM clinics, 3) conduct of a Pilot and Demonstration program for the development and evaluation of novel diagnostics, therapeutics, and outcome measures for these and additional 'on-deck' rare lung diseases, 4) provide clinical research training at RLDC clinical centers and attract new investigators to the field, and 5) develop rare lung disease educational materials for patients, medical providers, and the public.
Overlap: There is no overlap.

Title: COLA: A Pilot Clinical Trial of COX-2 inhibition in LAM and TSC (W81XWH-15-1-0511)
Effort: 1.44 Calendar Months (Co-I)
Supporting Agency: U.S. Army Medical Research Acquisition Activity
Grants Officer: Athansiou, Meropi (meropi.athanasiou.civ@mail.mil)
Performance Period: 09/15/2015-09/14/2018 (NCE)
Funding Amount: $172,173 direct costs per year
Project Goals: The goals of this study are 1) To investigate whether, in LAM patients, celecoxib is safe and well tolerated; 2) To investigate whether, in LAM patients, celecoxib treatment for 6 months results in improvement in LAM disease indicators; and 3) To investigate the potential value of a novel biomarker of LAM, quantitative measurement of TSC2 mutant LAM cells per ml of blood, to assess disease severity.
Specific Aims: Aim 1: To perform a clinical trial of the selective COX-2 inhibitor celecoxib for lymphangioleiomyomatosis (LAM). **Aim 2:** To investigate whether, in LAM patients, celecoxib treatment for 6 months results in improvement in LAM disease indicators. **Aim 3:** To investigate the potential value of a novel biomarker of LAM, quantitative assessment of TSC2 mutation in circulating LAM cells, to assess disease severity.
Overlap: There is no overlap.

CURRENT:
Title: Lymphatics and Lung Allograft Rejection (5R01HL130275-04)
Effort: 3.6 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Craig, Matt (matt.craig@nih.gov)
Performance Period: 07/01/2016-06/30/2021
Funding Amount: $275,663 direct costs per year
Project Goals: The goals of this proposal are to understand the functions of the lymphatic vasculature in acute lung allograft rejection.
Specific Aims: Aim 1. To identify the origin of lymphatic endothelial cells in lymphatic vessel regeneration after lung transplantation; **Aim 2.** To determine mechanisms whereby lymphangiogenesis protects against lung allograft rejection; **Aim 3.** To demonstrate that lymphatic

specific changes in lung tissue and peripheral blood can predict acute lung rejection and response to therapy.
Overlap: There is no overlap.

Title: LAMP: The LAM Microbiome Project (W81XWH-17-1-0469)
Effort: 1.2 Calendar Months (PI)
Supporting Agency: U.S. Army Medical Research Acquisition Activity
Grants Officer: Athansiou, Meropi (meropi.athanasiou.civ@mail.mil)
Performance Period: 09/30/2016-09/29/2020
Funding Amount: $58,025 direct costs per year
Project Goals: The goals of this study are 1) To investigate the LAM microbiome in early disease and 2) To investigate the LAM microbiome in LAM lung explanted at the time of transplant. The major goal is to establish the microbiome as a biomarker of disease progression or a therapeutic target.
Specific Aims: Aim 1: To define the respiratory tract microbiome in women with LAM with early lung disease.
Aim 2: To define the lung microbiome of explanted LAM lung.
Overlap: There is no overlap.

Title: Clinical Genetics and Screening for Pulmonary Fibrosis (5R01HL130974-04)
Effort: 0.6 Calendar Months (Co-I)
Supporting Agency: NIH/NHLBI
Grants Officer: Harabin, Andrea L. (andrea.harabin@nih.gov)
Performance Period: 01/01/2016-12/31/2019
Funding Amount: $307,326 direct costs per year
Project Goals: The goal of this proposal is to demonstrate the value of genetic testing for diagnostic and prognostic evaluation of patients with, or at risk for IPF. Recent studies also demonstrate that genetic testing may be a critical factor that can help guide early detection. We hypothesize that specific, known genetic variants confer variable prognosis in patients with pulmonary fibrosis (PF), and that targeted genetic testing will aid in patient counseling, early disease detection, and ultimately, earlier initiation of medical therapy.
Specific Aims: To assess these hypotheses we propose to address the following specific aims: Aim 1) Does targeted genetic testing aid in the diagnostic and prognostic evaluation of patients with pulmonary fibrosis? Aim 2) Does targeted genetic testing aid in early detection, and prognostication of populations at-risk for pulmonary fibrosis? and Aim 3) We will assess the psychosocial impact of genetic testing groups at-risk for pulmonary fibrosis.
Overlap: There is no overlap.

Title: The Molecular and Genetic Pathogenesis of LAM (5U01HL131022)
Effort: 1.38 Calendar Months (Co-I)
Supporting Agency: NIH/NHLBI
Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)
Performance Period: 09/21/2016-08/31/2020
Funding Amount: $65,388 direct costs per year
Project Goals: This U01 brings together a unique team of leaders in LAM research to address key unanswered questions with high clinical impact. First, what are the fundamental mechanisms leading to lymphangiogenesis in LAM? Second, can circulating LAM cell burden be quantitated

through "next generation" sequencing and used as a biomarker of LAM? Third, will finer dissection of the genetic basis of sporadic LAM reveal generalized low-level TSC2 mosaicism? Fourth, can biomarkers including VEGF-D and microRNA be used to develop personalized strategies for sirolimus dosing?
Specific Aims: The major goals of this project are: 1) to use freshly isolated circulating LAM cells and monocytic cells collected from serum of LAM patients at the NIH Clinical Center to determine the specific cell type and the cellular mechanism of VEGF-D overexpression in LAM, 2) to use next generation sequencing (NGS) to identify TSC1/TSC2 mutations in circulating LAM cells, and 3) to correlate the effect of sirolimus on serum microRNA, circulating LAM cells, VEGF-D and other lymphangiogenic factors, and indicators of mTORC1 activity, leading to the preliminary design of a combinatorial biomarker signature of sirolimus efficacy in LAM and enabling future studies of personalized dosing.
Overlap: There is no overlap.

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)
Effort: 0.6 Calendar Months (Co-Investigator)
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)
Performance Period: 09/15/2018-09/14/2022
Funding Amount: $761,103 direct costs year 1
Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: There is no overlap.

Title: Targeting the Angiotensin Receptor in TSC (W81XWH1910250)
Effort: 1.92 Calendar Months (PI)
Supporting Agency: DOD
Grants Officer: Ebony S. Simmons (ebony.s.simmons.civ@mail.mil)
Performance Period: 06/01/2019-05/31/2022
Funding Amount: $150,000 direct costs per year
Project Goals: The major goals of this project are to understand the role of AGTR1 in TSC2-deficient cell death Aim 1: To investigate the role of AGTR1 inhibition in TSC2-deficient cell growth in vivo
Specific Aims: Aim 2: To investigate AGTR1-dependent mechanisms of TSC2-deficient cell death in vitro.
Aim3: To investigate klotho-dependent TSC2-null cell death in vivo and to identify a klotho-dependent signature of LAM and TSC.
Overlap: There is no overlap.

PENDING:
Title: The Molecular and Genetic Pathogenesis of LAM (2U01HL131022)

Effort: 1.68 Calendar Months
Supporting Agency: NIH/NHLBI (PI: Henske) – (received a JIT)
Grants Officer: Grants Management Specialist: Livshin, Renee, 301-435-0174
Performance Period: 09/21/2019-08/31/2024
Funding Amount: $348,291 direct costs year 1
Project Goals: To investigate the molecular and genetic pathogenesis of LAM.
Specific Aims: Aim 1: To use freshly isolated circulating LAM cells and monocytic cells collected from serum of LAM patients at the NIH Clinical Center to determine the specific cell type and the cellular mechanism of VEGF-D overexpression in LAM. AIM 2: To use next generation sequencing (NGS) to identify TSC1/TSC2 mutations in circulating LAM cells and 3) to correlate the effect of sirolimus on serum microRNA, circulating LAM cells, VEGF-D and other lymphangiogenic factors, and indicators of mTORC1 activity, leading to the preliminary design of a combinatorial biomarker signature of sirolimus efficacy in LAM and enabling future studies of personalized dosing.
Overlap: There is no overlap.

PREVIOUS/CURRENT/PENDING SUPPORT:

SERHAN, CHARLES

PREVIOUS:
Title: Resolution Mechanisms in Acute Inflammation: Resolution Pharmacology (P01GM095467-05)
Effort: 4.2 calendar months
Supporting Agency: NIH/NIGMS
Grants Officer: Richard T. Okita (okitar@nigms.nih.gov)
Performance Period: 04/01/11 - 03/31/16
Funding Amount: $ 224,614 (Project 1) and $164,612 (Core B) direct costs per year
Project Goals: The overall novel hypothesis addressed is: Resolvins, protectins and maresins constitute a new genus of SPM that temporally regulate endogenous anti-inflammatory and pro-resolving pathways. SPM govern resolution via regulated leukocyte responses, enhanced mucosal defense and bacterial containment. These molecular events can be harnessed for novel resolution pharmacology to treat diseases.
Specific Aims: This P01 team consists of 3 projects, 2 scientific cores and an advisory unit focused on establishing LM-resolution metabolome, stereo-controlled synthesis of SPM and their specific mechanisms in resolution, anti-inflammatory and clearance pathways. Selected synthetic SPM will be scaled-up for demonstration of their unique mode of action in vivo in a resolution pharmacology core using experimental disease models.
Overlap: There is no overlap.

Title: Controlling Cancer With Aspirin-Triggered Stimulation of Resolution (R01CA170549-04)
Effort: 1.2 calendar months
Supporting Agency: NIH/NCI
Grants Officer: Asad Umar (asad.umar@nih.gov)
Performance Period: 09/18/12 - 07/31/16
Funding Amount: $103,750 direct costs per year
Project Goals: The overall goal of this project is to determine whether the anti-cancer activity of resolvins can be harnessed to eradicate cancer by an entirely novel approach, which manipulates endogenous pro-resolving mediators.
Specific Aims: In Aim 1 we will establish in animal models that AT-RvDs have broad anti-cancer activity and elucidate the cellular mechanisms of action that regulate the inflammation-clearing effect of resolvins. This will set the foundation for Aim 2, which is to determine whether aspirin's anti-cancer activity is mediated by AT-RvD1. To abrogate resolvin receptor activity we will use genetically engineered mice that lack the RvD1 receptor ALX/FPR-2 and a pharmacological antagonist of its receptor (ALX/FPR-2). Manipulating the resolvin pathway will also be achieved with transgenic (fat-1) mice, which have increased endogenous omega-3 fatty acids (the substrates of AT-RvDs). These studies lay the groundwork to optimize the resolvin pathway to inhibit or prevent cancer in preclinical studies for translation to humans. Thus, in Aim 3 we will compare the toxicity profiles of resolvins to aspirin (i.e. in gastric bleeding and aspirin-induced mucosal injury). To determine if resolvins can replace aspirin in chemoprevention experiments, we will recapitulate the human experience with aspirin using the murine model of ApcMin/+ colon carcinogenesis.
Overlap: There is no overlap.

Title: Research Development Program (Lipidomics Core)
Effort: 0.24 calendar months
Supporting Agency: Cystic Fibrosis Foundation
Grants Officer: N/A
Performance Period: 07/01/08 - 06/30/15
Funding Amount: $50,000 direct costs per year
Project Goals: The Lipidomics Core will facilitate programmatic interest in the regulation and dysregulation of inflammation in the CF airway, ongoing CFF-RDP projects (including current Pilot and Feasibility Projects), interest in lipid metabolism and mediators as biomarkers of disease status, and translational interest in lipid mediators as therapeutics for CF lung disease.
Specific Aims: N/A
Overlap: There is no overlap.

Title: Carbon Monoxide: Novel Opportunities for Therapy (5P01HL108801-05)
Effort: 3 calendar months
Supporting Agency: NIH/NHLBI
Grants Officer: Andrea L. Harabin (andrea.harabin@nih.gov)
Performance Period: 08/15/11 - 06/30/16
Funding Amount: $260,000 (Project 4) and $120,000 (Core C) direct costs per year
Project Goals: Project 4 will test the following hypothesis: Local activation of tissue resolution programs by inhaled CO involves production of novel anti-inflammatory and pro-resolving lipid mediators that enhance the clearance of apoptotic cells and microbes. CO activates the production of the new genus of SPM including resolvins and lipoxins and reduces biosynthesis of proinflammatory lipid mediators. SPM and CO act together to govern responses required for limiting inflammation and enhancing microbial killing and resolution.
Specific Aims: Project 4 will address 4 specific aims: 1. Determine the impact of CO on biosynthesis of lipid mediators and SPM during acute inflammation. 2. SPM activation of heme oxygenase-1 (HO-1). 3. Impact of CO and SPM in resolution of sepsis and second organ I/R acute lung injury; and 4. LM-lipidomic profiling with sepsis vs. ALI patient library/bank.
Overlap: There is no overlap.

Title: Blood Cell Lipoxygenase Products -- Formation and Action (2R01GM38765-31)
Effort: 3.6 calendar months
Supporting Agency: NIH/NIGMS
Grants Officer: Richard T. Okita (okitar@nigms.nih.gov)
Performance Period: 08/01/14 - 07/31/18
Funding Amount: $250,000 direct costs per year
Project Goals: We propose to test the following hypothesis: Local specialized pro-resolving mediators (SPM) produced by exudate phagocytes required for timely resolution are stimulated by neuronal signals. Resolvins, specifically resolvin D2 (RvD2), a newly elucidated resolvin, is a potent agonist that governs local phagocyte resolution responses via novel pro-resolving receptors required for homeostasis and effective microbial clearance.
Specific Aims: The following specific aims will be carried out: 1. Vagus activation of innate phagocytes, resolvins and resolution pathways; 2. Novel resolvin D2 pro-resolving receptor circuit; 3. Functional validation of RvD2-specific pro-resolving receptors; 4. Pro-resolving receptors – human phagocyte panel in disease.
Overlap: There is no overlap.

Title: Novel Therapies for Cigarette Smoke Induced Lung Injury (R01HL120908-04)
Effort: 0.6 calendar months
Supporting Agency: NIH/NHLBI
Grants Officer: Lisa Postow (lisa.postow@nih.gov)
Performance Period: 08/15/14 - 05/31/18
Funding Amount: $23,480 direct costs per year
Project Goals: Our overall hypothesis is that pro-resolving lipid mediators (PRMs) will have profound anti-inflammatory and pro-resolving effects on both acute and chronic lung injury, and that treatment with pro-resolving mediators to promote resolution is a novel and important therapeutic goal for inflammatory diseases caused by cigarette smoking.
Specific Aims: To investigate this hypothesis we have proposed the following specific aims. Specific Aim 1. Determine PRMs with the greatest efficacy at promoting resolution of acute inflammation in vitro and in vivo and determine their mechanism of action using primary human lung cells and a mouse model of cigarette smoke-induced acute lung inflammation. Specific Aim 2. Determine changes in the PRM profile of human samples with smoke-induced chronic lung disease, and evaluate the ability and mechanism by which PRMs prevent and treat lung tissue destruction in a mouse model of chronic smoke exposure.
Overlap: There is no overlap.

Title: Mechanisms of Resolvin E1 in Periodontal Regeneration (R01DE025020-04)
Effort: 1.2 calendar months
Supporting Agency: NIH/NIDCR
Grants Officer: Nadya L. Lumelsky (nadya.lumelsky@nih.gov)
Performance Period: 05/01/15 - 04/30/19
Funding Amount: $75,000 direct costs per year
Project Goals: The central hypothesis is that resolution of inflammation pathways and mediators can be harnessed to control inflammation in periodontal tissues enabling regeneration and reconstruction. We have demonstrated that delivery of lipoxins and resolvins greatly enhances tissue regeneration by control of inflammation. Resolvins also have actions beyond control of neutrophils including receptor-mediated control of osteoclast and osteoblast function in wound healing and bone regeneration.
Specific Aims: We will identify key endogenous control mechanisms for bone formation induced by RvE1 using specific RvE1 receptor knock-out (KO) and receptor over-expressing transgenic mice, determine the basis for bone cell responses to RvE1 by elucidation of signal anabolic pathways that promote osteoblast mediated bone formation and limit osteoclast activity, and unravel the complexities of lipid mediator synergy and characterize hetero- specific resolution agonist amplification by determining pro and anti-inflammatory lipid mediator profiles induced by RvE1.
Overlap: There is no overlap.

CURRENT:
Title: Resolution Mechanisms in Acute Inflammation: Resolution Pharmacology (P01GM095467-09)
Effort: 6.0 calendar months
Supporting Agency: NIH/NIGMS
Grants Officer: Martha Garcia (Martha.garcia@nih.gov)
Performance Period: 04/01/16 - 03/31/21

Funding Amount: $230,285 (Project 1) and $149,929 (Core B) direct costs per year
Project Goals: Our overall mission in this renewal is to systematically elucidate the structures and functions of novel mediators in resolution and tissue regeneration. Our strategic plan includes lipid mediator (LM)-SPM-metabololipidomics with resolution and regeneration indices to interrogate inflammatory exudates and tissues coupled with total organic synthesis of SPM and SPM-SC standards to validate structure-function. The overarching novel hypothesis to be addressed by each project of this renewal requires a highly multi-disciplinary team and approach.
Specific Aims: Together, we shall test the following: Infectious inflammatory exudates evoked by tissue injury, surgical trauma and infection emit potent soluble chemical mediators locally such as SPM and their newly identified sulfido-conjugates that actively orchestrate resolution of inflammation, enhance microbial killing and clearance, as well as tissue regeneration. These new molecular resolution programs are essential for host defense and dictate severity and recovery intervals.
Overlap: There is no overlap.

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)
Effort: No measurable effort (other significant contributor)
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)
Performance Period: 09/15/18 - 09/14/22
Funding Amount: $761,103 direct costs year 1
Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: There is no overlap.

Title: Blood Cell Lipoxygenase Products -- Formation and Action (R01GM038765-33)
Effort: 3.6 calendar months
Supporting Agency: NIH/NIGMS
Grants Officer: Martha Garcia (Martha.garcia@nih.gov)
Performance Period: 08/01/18 - 07/31/22
Funding Amount: $250,000 direct costs per year
Project Goals: Long-term objectives include providing novel approaches for clinicians to activate resolution and improve treatment of excessive inflammation.
Specific Aims: This project will test a new hypothesis: Coagulation of blood temporally activates a specific cluster of SPM (RvE1, RvD1, RvD5, LXB4 and MaR1) linking coagulation to resolution and innate host defense. Together with resolvins and their receptors, MaR1 is a potent agonist governing local phagocyte resolution responses via new receptors required for effective microbial killing.
Overlap: There is no overlap.

Title: Mechanisms of Pro-Resolving Mediators in Periodontal Regeneration (R01DE025020-05)

Effort: 0.3 calendar months
Supporting Agency: NIH/NIDCR
Grants Officer: Nadya L. Lumelsky (nadya.lumelsky@nih.gov)
Performance Period: 07/01/19 - 06/30/24
Funding Amount: $48,198 direct costs per year
Project Goals: Characterizing the biomimetic properties of SPMs in humans is hampered by a lack of suitable large animal models. There is a critical need for a validated large animal regeneration model to test therapeutic potential of SPMs for translation to humans. Our goal is to determine the pathways to regeneration that control local inflammation and enhance mesenchymal stem cell differentiation into connective tissues, including bone.
Specific Aims: The aims of this proposal are: 1) Direct evidence for SPM production by Yorkshire miniature pig periodontal ligament stem cells (mpPDLSC), 2) Determine stem cell function in human vs. miniature pig, as well as 3) Demonstration in Miniature Pig Periodontal Regeneration. The scope of this subcontract focuses on LC-MS-MS based profiling of lipid mediators via metabololipidomics, validation of synthetic mediators to be used in these experiments, as well as preparing pro-resolving nanomedicine for in vivo studies in mini-pigs. **Overlap:** There is no overlap.

Title: Vitamin D and Fish Oil for Autoimmune Disease and Inflammation (R01AR059086-07)
Effort: 0.58 calendar months
Supporting Agency: NIH/NIAMS
Grants Officer: James Witter (witterj@mail.nih.gov)
Performance Period: 04/01/18 - 03/31/22
Funding Amount: $12,529 direct costs per year
Project Goals: This nationwide double-blind, placebo-controlled, randomized clinical trial will test the potential benefits of vitamin D and marine omega-3 fatty acid supplements for the prevention of autoimmune diseases, investigating the time course of their effects and subgroups most affected, as well as the potential generation of novel lipid mediators that can promote inflammation resolution.
Specific Aims: With this renewal grant, we will complete the 5 pre-specified years and a 2 year observational extension, critically important given the long latency of autoimmune disease onset. Continued follow-up will improve statistical power for detecting preventive effects on autoimmune disease incidence, and will enable investigations of effects over time and effect modification by baseline factors and biomarkers. We hypothesize that there will be a delayed reduction in autoimmune disease, and that the largest preventive effects will be among those with high systemic inflammation, including the obese and those with elevated baseline biomarkers of inflammation. In this renewal, we also will test for changes in "Specialized Pro-Resolving Mediators" (SPM), novel omega-3 fatty acid-dependent lipids responsible for inflammation resolution. We will employ cutting-edge quantitative liquid chromatography-tandem mass spectroscopy to extend understanding of the biological mechanisms by which omega-3 fatty acids influence inflammation resolution and potentially autoimmune disease pathogenesis. Given the ongoing NIH-funded VITAL trial infrastructure, our strong multidisciplinary research team, and success with prior large mail-based trials and cohort studies, with continued funding these investigations will furnish robust and definitive results with important public health ramifications.
Overlap: There is no overlap.

PENDING:
Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS

Effort: 0.24 calendar months in years 2-4
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 07/01/20 - 06/30/24
Funding Amount: $348,291 direct costs year 1
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

Title: Precision Electric Medicine for Resolution of Inflammation and Pain
Effort: 6.6 calendar months in year 1, 7.2 calendar months in years 2-5
Supporting Agency: NIH (Director's Pioneer Award)
Grants Officer: N.A.
Performance Period: 09/30/20 - 07/31/25
Funding Amount: $700,000 annual direct costs
Project Goals: The promise of this exceptionally innovative and transformative approach is to assemble a prototype electrical vagal stimulator (EVS) with demonstrated ability to activate resolution of inflammation and reduce pain via novel vagus-derived pro-resolving molecules and compare these to vagus-derived SPM, a high-risk goal that addresses current public health needs with cross-cutting science that has potential to be broadly impactful.
Specific Aims: 1) Elucidation of novel structures of bioactive lipid mediators (LM) produced by isolated vagus and direct comparison of these to vagal specialized pro-resolving mediators (SPM); 2) Establish specific electrical current(s) needed to target vagal production of novel pro-resolving signals (PRS) and create a prototype to test this in aging mice and human isolated vagus; *and* 3) Demonstrate the prototype's ability to activate resolution programs in mice and humans to reduce pain and inflammation.
Overlap: There is no overlap.

ACTIVE/PENDING/PREVIOUS

KAREN WELTY-WOLF

ACTIVE

THIS AWARD

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (Piantadosi)
Effort: 20% / 2.4 calendar months
Supporting Agency: Department of Defense 181691-02/W81XWH1810667
Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Performance Period: 09/15/2018 – 09/14/2022
Funding Amount: $211,300 Direct Costs**,** $329,494 Total Costs
Goals: The major goal of this Department of Defense Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award is to advance the field of carbon monoxide (CO) therapeutics in a Phase II interventional trial of inhaled CO in subjects with the acute respiratory distress syndrome (ARDS).
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS
Overlap: None

PREVIOUS (last 5 years)

Title: Novel Dialysis-Like Therapeutics in Sepsis-induced Shock and Organ Failure (Welty-Wolf)
Effort: 20% / 2.40 calendar months
Supporting Agency: Defense Advanced Research Projects Agency HR0011-15-2-0057
Grants Officer: 675 North Randolph St. Arlington, VA. 22203-2114
Performance Period: 9/28/2015-05/31/2018
Funding Amount: $620,146
Goals: The main goals of this project are to determine the efficacy and safety of hemadsorption therapy during
pneumococcal sepsis using a novel DLT device, measuring effect on clearance of bacteria and cytokines from
the blood.
Specific Aims: 1. Determine the efficacy of hemadsorption therapy using a novel DLT device.
2. Determine the safety of DLT hemadsorption in baboons with pneumococcal pneumonia and sepsis.
Overlap: None

Title: Project 2: Regulation of Mitochondrial Quality Control by Heme Oxygenase-1 System in Sepsis (Piantadosi)
Effort: 78% / 9.48 calendar months
Supporting Agency: Brigham and Women's Hospital 107287

Grants Officer: Paul J Anderson, 75 Francis St. Boston MA 02115
Performance Period: 08/15/2011 – 06/30/2017
Funding Amount: $322,412
Goals: The overall goal is to demonstrate that HO/CO-induced transcriptional activation of mitochondrial biogenesis in sepsis generates an anti-inflammatory response through NFE2l2 and NRF-1 that is implemented by IL-10 and/or SOCS3 up-regulation, and which suppresses pro-inflammatory cytokine production and activates mitophagy.
Specific Aims: The specific aims of this project are to: i) elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection, ii) identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI, and iii) provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI at the next Cycle II of the translational PPG program.
Overlap: None

Title: Biomarkers to discriminate bacterial pneumonia vs influenza and to distinguish pneumococcal colonization vs infection (Ginsburg)
Effort: 3% / 0.36 calendar months
Supporting Agency: Bill and Melinda Gates Foundation OPP1017554
Grants Officer: 440 5th Ave N, Seattle, WA. 98109
Performance Period: 07/25/2011 – 09/30/2015
Funding Amount: $2,470,010
Goals: *Major goal*: To test biomarkers to discriminate bacterial pneumonia vs influenza and to distinguish pneumococcal colonization vs infection.
Overlap: None

PENDING

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Effort: 25%/ 3.0 Calendar Months (Site-PI) Years 2-4
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 07/01/2020 – 06/30/2024
Funding Amount: $348,291 direct costs year 1
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary

to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

VETERANS ADMINISTRATION

ACTIVE

Title: Mechanisms of Alveolar Mitochondrial Damage and Resolution in Pneumonia
Time Commitment: 25%, 3 calendar months
Supporting Agency: Veterans Administration
Contact Name and Address: Veteran Administration, Box 004289-01A2
Performance Period: 10/01/2019-09/30/2023
Level of Funding: $660,000 Direct Costs
Goals/Aims: The goal of this project is to achieve novel concepts for host activation of the two main MQC pathways and how they participate in limiting ALI progression and can be translated into treatments to diminish the morbidity, mortality, and health care utilization costs of ICU patients.
Overlap: None

PENDING

None

PREVIOUS (last 5 years)

None

PREVIOUS/CURRENT/PENDING SUPPORT:

CLAUDE PIANTADOSI

ACTIVE

Title: Mitochondrial quality control and alveolar damage resolution after acute lung injury (Piantadosi)
Effort: 20.5% / 2.46 calendar months
Supporting Agency: NIH 1R01-HL135239
Grants Officer: Neil Raj Aggarwal, M.D., National Heart, Lung, and Blood Institute (NHLBI), 6701 Rockledge Drive, Bethesda, MD 20892-7952
Funding Amount: $250,000 Direct Costs
Performance Period: 08/01/2017 – 06/30/2021
Goals: Our goal is proof-of-principle for the idea that loss of mitochondrial QC regulation and cell proliferation lead to persistent epithelial barrier dysfunction and fibrosis.
Specific Aims: Aim 1) Measure and localize oxidant damage in lung parenchyma and AT2 cell mitochondria (specifically mtDNA oxidation) in ALI/pneumonia in mice and its impact on mitochondrial QC regulation by HO-1/CO and a) AT2 cell apoptosis, b) resolution of alveolar inflammation, and c) alveolar barrier dysfunction. Aim 2) Test how HO-1 induction of the mitochondrial QC network a) activates mitophagy, b) accelerates AT2 cell proliferation and trans-differentiation into type I epithelium, and c) prevents lung fibrosis after ALI/pneumonia. Aim 3) Demonstrate whether strategies that activate mitochondrial QC will reverse loss of lung protection in ALI/pneumonia in mice with conditional knockout (CKO) of HO-1 or CKO of NRF-1 in AT2 cells using the approaches in Aim 1.
Overlap: None

Title: Oxidative tissue damage mitigation after exposure to HBO2 using FDA approved anti-epileptic drugs (AEDs)
Effort: 38%/4.56 calendar months
Supporting Agency: Office of Naval Research N00014-18-1-2702
Grants Officer: Sandra Chapman, M.D., Office of Naval Research
875 N. Randolph Street, Suite 1425, Arlington, VA 22203-1995
Performance
Funding Amount: $718,773 Total Costs
Performance Period: 08/01/2018 – 07/31/2020
Goals: The goal of this project is to show that combinations of two AED from different classes will prevent HBO2 seizures and limit oxidative tissue damage.
Specific Aims:
Aim 1: Measure oxidative tissue and mitochondrial damage by 5ATA HBO2 in mouse forebrain including hippocampus and hindbrain using standard biochemical tests under conditions of A) Control, B) HBO2, C) AED combinations alone, and D) HBO2 plus AED combinations.
Aim 2: Measure basic neurotransmitter levels in mouse forebrain including hippocampus and hindbrain under conditions of A) Control, B) HBO2, C) AED combinations only, and D) HBO2 plus AED combinations.

Aim 3: Measure inflammatory activity in mouse forebrain and hindbrain, lung parenchyma, and mouse plasma and compare the four conditions outlined in Aims 1 and 2.
Aim 4: Measure cell death at days 1 and 7 in the brain and compare it with changes in motor coordination by parallel bar.
Overlap: None

Title: A Randomized Phase II Clinical Trial of L-Citrulline to improve Asthma Control in Obese Late Onset Asthma
Effort: 5% / 0.6 calendar months
Supporting Agency: University of Colorado / NIH
Grants Officer: Fernando Holguin, M.D., Allergy & Asthma Clinic – Anschutz, 1635 Aurora Ct 6th floor, Aurora, CO 80045
Funding Amount: $234,262 Direct Costs
Performance Period: 04/01/2019-03/31/2024
Goal: Our goal as the subcontractor is to analyze and interpret data, co-author and lead manuscripts, and support the general scientific oversight of the project.
Specific Aim:
Aim 1: To conduct a randomized clinical trial (N = 114) to evaluate the efficacy of L-citrulline supplementation for patients with late onset obese asthma that are not controlled with ICS or ICS/LABA and/or LAMA therapy. **Overlap:** None

Title: Interdisciplinary Training Program in Lung Disease (Piantadosi/Palmer)
Effort: 0% / 0 calendar months
Supporting Agency: National Institutes of Health/ National Heart, Lung, and Blood Institute T32 HL007538 **Grants Officer:** Sandra Colombini Hatch, M.D., Lung Biology and Disease Program Division of Lung Diseases, National Heart, Lung, and Blood Institute, 6701 Rockledge Drive, Rockledge ll Suite 10124, MSC 7952, Bethesda, MD
20892-7952 **Performance Period:** 07/01/2015 –
0/3/31/2020
Funding Amount: $418,212 Direct Costs
Goals: The major goals for this proposal are to train postdoctoral trainees to acquire the basic knowledge, understanding, and skills for an academic career emphasizing research in the general field of lung diseases.
Specific Aims: N/A
Overlap: None

THIS AWARD
Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (Piantadosi)
Effort: 25% / 3 calendar months
Supporting Agency: Department of Defense 181691-02/W81XWH1810667
Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Performance Period: 09/15/2018 – 09/14/2022
Funding Amount: $211,300 Direct Costs**,** $329,494 Total Costs
Goals: The major goal of this Department of Defense Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award is to advance the field of carbon monoxide (CO) therapeutics in a Phase II interventional trial of inhaled CO in subjects with the acute respiratory distress syndrome (ARDS).

Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS
Overlap: None

PREVIOUS (last 5 years)

Title: Critical Molecular Targets for the Toxic Effects of Hyperbaric Oxygen and a Novel Pharmacological
Approach for Preventing Acute Toxicity (Piantadosi)
Effort: 20% / 2.4 calendar months
Supporting Agency: Office of Naval Research N00014-15-1-2072
Grants Officer: Lawrence Schuette, One Liberty Center 875N. Randolph Street, Suite 1425, Arlington, VA. 22203-1995
Performance Period: 04/01/2015 – 06/30/2019
Funding Amount: $690,295
Goals: To determine the role of molecular targets in key brain regions, drugs would be delivered to striatum, hippocampus and hypothalamus by microdialysis in rats, and the effluent dialysate would be collected for analysis of markers of oxidative and nitrosative attack.
Specific Aims: Our first objective, drugs would be carefully selected, based on experience gained from our previous studies of CNS O2 toxicity as well as on the clinical literature for epilepsy. Up to two drugs from each category would be tested individually. For our second objective, the most effective individual drugs would be tested in pairs. Our third objective, the most promising single drug or two- or three-drug combinations would be tested in instrumented animals so that appropriate physiological parameters could monitored to elucidate and confirm the mechanism(s) involved in the protective response.
Overlap: None

Title: Novel Dialysis-Like Therapeutics in Sepsis-induced Shock and Organ Failure (Welty-Wolf)
Effort: 10% / 1.2 calendar months
Supporting Agency: (DARPA) Defense Advanced Research Projects Agency HR0011-15-2-0057
Grants Officer: 675 North Randolph St. Arlington, VA. 22203-2114
Performance Period: 09/28/2015 – 05/31/2018
Funding Amount: $620,146
Goals: The main goals of this project are to determine the efficacy and safety of hemadsorption therapy during pneumococcal sepsis using a novel DLT device, measuring effect on clearance of bacteria and cytokines from the blood.
Specific Aims:
1. Determine the efficacy of hemadsorption therapy using a novel DLT device.
2. Determine the safety of DLT hemadsorption in baboons with pneumococcal pneumonia and sepsis. **Overlap:** None

Title: Redox Regulation of Lung Mitochondrial Biogenesis in Sepsis/Pneumonia (Piantadosi)
Effort: 26% / 3.36 calendar months

Supporting Agency: NIH/NIAID 4R01-AI095424-05
Grants Officer: Ted Williams, 6120 Executive Blvd, EPS Suite 243, MSC 7150, Bethesda, MD 20892
Performance Period: 07/01/2012 – 06/30/2017
Funding Amount: $250,000
Goals: To understand how the genetic program of mitochondrial biogenesis mediates lung protection through anti-inflammatory gene expression, suppression of inflammatory interleukin-1b production, and activates mitophagy leading to resolution of lung capillary leak in ARDS patients.
Specific Aims: Aim 1: Determine whether Nfe2l2 and NRF1 induction of lung mitochondrial biogenesis in murine S. aureus sepsis and pneumonia up-regulates Socs3 and Il10 anti-inflammatory gene expression, suppresses caspase1 cleavage and IL-1 production and mitigates lung inflammation and ALI. Aim 2: Use gain and loss of function studies to determine whether Nfe2l2 and NRF1 induction of lung of mitochondrial biogenesisregulates the autophagy genes Bnip3 and Atg5 and b) activates pro- survival mitophagy through HO-1/CO-related mitochondrial ROS generation in murine S. aureus pneumonia. Aim 3: Assess the extent, location, and relationship of mitochondrial biogenesis to mitophagy in the alveolar epithelium of human ALI/ARDS patients compared with healthy human lung.
Overlap: None

Title: Project 2: Regulation of Mitochondrial Quality Control by Heme Oxygenase-1 System in Sepsis (Piantadosi)
Effort: 22.50% / 2.7 calendar months
Supporting Agency: Brigham and Women's Hospital P01 HL108801
Grants Officer: Christopher Dunleavy, 75 Francis Street, Boston, MA 02115
Performace Period: 08/15/2011 – 06/30/2017
Funding Amount: $322,412
Goals: The overall goal is to demonstrate that HO/CO-induced transcriptional activation of mitochondrial biogenesis in sepsis generates an anti-inflammatory response through NFE2l2 and NRF-1 that is implemented by IL-10 and/or SOCS3 up-regulation, and which suppresses pro-inflammatory cytokine production and activates mitophagy.
Specific Aims: The specific aims of this project are to: i) elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection, ii) identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI, and iii) provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI at the next Cycle II of the translational PPG program.
Overlap: None

Title: Developing a Non-Human Primate Model of Bacterial Pneumonia and Discovery of Novel Diagnostic Biomarkers (Ginsburg)
Effort: 0.12 calendar months
Supporting Agency: Bill and Melinda Gates Foundation OPP1017554
Grants Officer: 440 5th Ave N, Seattle, WA. 98109
Performance Period: 07/25/2011 – 09/30/2015
Funding Amount: $2,470,009

Goals/Aims: Development of improved, inexpensive and easy-to-use rapid diagnostics that could be used to accurately distinguish, in non-invasively collected clinical specimens, bacterial pneumonia from asymptomatic bacterial colonization in the presence or absence of concomitant virus-associated pneumonia would represent a major advance in the health of children worldwide and have a significant impact on improving the clinical management and outcome of acute pneumonia in children in these settings.
Overlap: None

PENDING

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Effort: 5%/ 0.60 Calendar Months (Co-Investigator) Years 2-4
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 07/01/20 – 06/30/24
Funding Amount: $348,291 direct costs year 1
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

VETERANS ADMINISTRATION

ACTIVE

Title: Mechanisms of Alveolar Mitochondrial Damage and Resolution in Pneumonia
Effort: 35%, 4.2 calendar months
Supporting Agency: Veterans Administration
Grants Officer: Veteran Administration, Box 004289-01A2
Performance Period: 10/01/2019-09/30/2023
Funding Amount: $660,000 Direct Costs
Goals/Aims: The goal of this project is to achieve novel concepts for host activation of the two main MQC pathways and how they participate in limiting ALI progression and can be translated into treatments to diminish the morbidity, mortality, and health care utilization costs of ICU patients.
Overlap: None

PENDING

None

PREVIOUS (last 5 years)

None

PREVIOUS/CURRENT/PENDING SUPPORT

KRAFT. BRYAN

ACTIVE

Title: Role of S-nitrosothiols in Akt1 signaling and pneumonia resolution (Kraft)
Time Commitment: 75% / 9.0 calendar months
Supporting Agency: National Institutes of Health (5K08-HL130557)
Contact Name and Address: Allison Moyal, RKL2 Bldg, Room 7144, 6701 Rockledge Drive, Bethesda, MD 20817;
Phone #: 301-827-8036; Email: allison.moyal@nih.gov
Performance Period: 01/15/17-12/31/2021
Level of Funding: $109,405 Direct Costs**,** $118,157 Total Costs
Goals: The major goal of this project is the identification of these phosphatases as novel, pharmacologic targets for treating pneumonia-induced ALI.
Specific Aims: 1) Determine if S-nitrosylation of (a) PTEN and/or (b) PHLPP activate Akt1 and mitochondrial biogenesis in lung AT2 cells; and 2) Determine if pharmacologic SNO augmentation can accelerate resolution of ALI following murine S. aureus pneumonia. This work is expected to yield important insight into why endogenous mechanisms may not be sufficient to resolve severe pneumonia with ALI as well as novel regulatory mechanisms of mitochondrial biogenesis that could be pharmacologically exploited to accelerate pneumonia resolution.
Overlap: None

THIS AWARD
Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Time Commitment: 20% / 2.4 calendar months
Supporting Agency: Department of Defense 181691-02/W81XWH1810667
Contact Name and Address: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Performance Period: 09/15/2018 – 09/14/2022
Level of Funding: $211,300 Direct Costs**,** $329,494 Total Costs
Goals: The major goal of this Department of Defense Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award is to advance the field of carbon monoxide (CO) therapeutics in a Phase II interventional trial of inhaled CO in subjects with the acute respiratory distress syndrome (ARDS).
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS
Overlap: None

PENDING

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Effort: 20%/ 2.4 Calendar Months (Co-Investigator) Years 2-4
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 07/01/2020 – 06/30/2024
Funding Amount: $348,291 direct costs year 1
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PAST 5 YEARS

Title: Novel Dialysis-Like Therapeutics in Sepsis-induced Shock and Organ Failure (Welty-Wolf)
Time Commitment: 30% / 3.60 calendar months
Supporting Agency: Defense Advanced Research Projects Agency HR0011-15-2-0057
Contact Name and Address: 675 North Randolph St. Arlington, VA. 22203-2114
Performance Period: 09/28/2015 – 05/31/2018
Level of Funding: $620,146
Goals: The main goals of this project are to determine the efficacy and safety of hemadsorption therapy during pneumococcal sepsis using a novel DLT device, measuring effect on clearance of bacteria and cytokines from the blood.
Specific Aims:
Aim 1: Determine the efficacy of hemadsorption therapy using a novel DLT device.
Aim 2: Determine the safety of DLT hemadsorption in baboons with pneumococcal pneumonia and sepsis.

Title: Project 2: Regulation of Mitochondrial Quality Control by Heme Oxygenase-1 System in Sepsis (Piantadosi)
Time Commitment: 25% / 3.0 calendar months
Supporting Agency: Brigham and Women's Hospital 107287
Contact Name and Address: Paul J Anderson, 75 Francis St. Boston MA 02115
Performance Period: 08/15/2011 – 06/30/2017
Level of Funding: $322,412

Goals: The main goal of this project is prove that a pathway exists, which would mean that implementation of a process of mitochondrial quality control in otherwise viable cells can be instituted under safeguard from further molecular damage by unregulated local inflammatory responses.
Specific Aims:
Aim 1: Elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection,
Aim 2: Identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI
Aim 3: Provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI at the next Cycle II of the translational PPG program.

Title: Developing a Non-Human Primate Model of Bacterial Pneumonia and Discovery of Novel Diagnostic Biomarkers (Ginsburg)
Time Commitment: 1% / 0.12 calendar months
Supporting Agency: Bill and Melinda Gates Foundation OPP1017554
Contact Name and Address: 440 5th Ave N, Seattle, WA. 98109
Performance Period: 07/25/2011 – 09/30/2015
Level of Funding: $2,470,009
Goals/Aims Development of improved, inexpensive and easy-to-use rapid diagnostics that could be used to accurately distinguish, in non-invasively collected clinical specimens, bacterial pneumonia from asymptomatic bacterial colonization in the presence or absence of concomitant virus-associated pneumonia would represent a major advance in the health of children worldwide and have a significant impact on improving the clinical management and outcome of acute pneumonia in children in these settings.

ACTIVE/PENDING/PREVIOUS

DAVIES, JOHN

ACTIVE

Title: Prospective trial to validate safety of Hemolung Respiratory Assist System for COPD patients (MacIntyre)
Effort: 10% / 1.2 calendar months
Supporting Agency: Alung Technologies
Contact Name and Address: Marci Halevi, Senior Director, Clinical Trial Operations, ALUNG Technologies, Inc., 2500 Jane Street, Suite 1, Pittsburgh, PA, Phone #: 917-912-2510; Email: mhalevi@alung.com
Performance Period: 06/1/2018 – 05/31/2023
Level of Funding: $581,720 Direct Costs**,** $742,222 Total Costs
Goals: To demonstrate the safety and efficacy of using the Hemolung RAS to provide low-flow ECCO2R as an alternative or adjunct to invasive mechanical ventilation versus standard of care invasive mechanical ventilation alone to increase ventilator-free days for COPD patients who require respiratory support due to an acute exacerbation of their COPD.
Specific Aims: To validate the safety and efficacy of the Hemolung Respiratory Assist System (RAS) for COPD patients experiencing acute exacerbations requiring ventilatory support.
Overlap: None

THIS AWARD
Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (Piantadosi)
Effort: 40% / 4.8 calendar months
Supporting Agency: Department of Defense 181691-02/W81XWH1810667
Contact Name and Address: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Performance Period: 09/15/2018 – 09/14/2022
Level of Funding: $211,300 Direct Costs**,** $329,494 Total Costs
Goals: The major goal of this Department of Defense Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award is to advance the field of carbon monoxide (CO) therapeutics in a Phase II interventional trial of inhaled CO in subjects with the acute respiratory distress syndrome (ARDS).
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS
Overlap: None

PENDING

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS

Effort: 33.33% /4.0 calendar months (Clinical Research Coordinator) Years 2-4
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Performance Period: 07/01/20 – 06/30/24
Funding Amount: $348,291
Project Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PREVIOUS (Past 5 years)

None

PREVIOUS/CURRENT/PENDING SUPPORT:

VATSAAS, CORY

CURRENT:

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Effort: 2% /0.24 calendar months (Co-Investigator)
Supporting Agency: Department of Defense 181691-02/W81XWH1810667
Name and address of Contracting/Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil
Funding: $211,300 Direct Costs, 329,494 Total Costs
Performance Period: 09/15/2018 – 09/14/2022
Goals: The major goal of this Department of Defense Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award is to advance the field of carbon monoxide (CO) therapeutics in a Phase II interventional trial of inhaled CO in subjects with the acute respiratory distress syndrome (ARDS).
Specific Aims: Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS **Aim 2:** To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS
Overlap: None

PENDING:

None

PREVIOUS:

None

OVERLAP:

None

PREVIOUS/CURRENT/PENDING SUPPORT:

VIDAL MELO, MARCOS

PREVIOUS (last five years)

Project Title: A Prospective, Double-Blind, Randomized, Parallel Design Study to Compare the Hemodynamic and Respiratory Variations during Laparoscopic Surgery in Patients with and without Deep Neuromuscular Blockade
Time Commitment: 0.12 Cal. Mos.
Supporting Agency: Clinical Trial Research Agreement (Vidal Melo); Merck Sharp & Dohme Corp
Funding Agency's Contracting/Grants Officer (name/address): Alfred Saah, MD, MPH; Merck Sharp & Dohme, 351 North Sumneytown Pike, UG3CD-28, North Wales, PA 19454
Performance Period: 12/13/2013 – 12/12/2016
Funding Amount: $23,709
Brief Description of Project's Goals: This study addresses the effects of depth of muscle relaxation during laparoscopic surgery on the process of intraoperative lung derecruitment, central and peripheral gas exchange impairment, and cardiovascular function.
List of Specific Aims: Specific Aim 1: To quantify the dependence of hemodynamic parameters and cardiovascular support on two different depth levels of NMB before, during and after pneumoperitoneum. Specific Aim 2: To determine the impact of two different depth levels of NMB on respiratory mechanics, gas exchange, and oxygen transport to tissues during laparoscopic surgery. Specific Aim 3: To determine the required mean intra-abdominal pressure during laparoscopic surgery with and without deep NMB.
Project Role: PI
Overlap: None

Project Title: Effect of Prone Position on Ventilation-Induced Lung Injury
Time Commitment: 0.36 Cal. Mos.
Supporting Agency: 5R01-HL094639-05 (Musch); NIH-NHLBI
Funding Agency's Contracting/Grants Officer (name/address): Charmaine Parsad, RM Specialist; parsadrc@mail.nih.gov
Performance Period: 09/01/2010 – 07/31/2016 (NCE)
Funding Amount: $246,723
Brief Description of Project's Goals: To test whether promoting uniform lung inflation and tidal expansion by prone positioning reduces neutrophil metabolic activation.
List of Specific Aims: Specific Aim 1: To investigate the effectiveness of the prone position in decreasing the severity and topographical heterogeneity of VILI-induced neutrophil metabolic activation. Specific Aim 2: To investigate whether the prone position decreases neutrophil activation in dorsal regions of mechanically ventilated saline-lavaged lungs via a reduction of regional specific tidal expansion. Specific Aim 3: By imposing a graded increase in tidal volume, we will test if higher tidal volumes can be applied to the prone than to the supine saline-lavaged lung without augmenting neutrophil activation.
Project Role: Co-Investigator
Overlap: None

Project Title: PET/MRI Imaging of Neuroaxial Inflammation in Sciatica Patients
Time Commitment: 0.12 Cal. Mos.
Supporting Agency: 5R21-NS082548-02 (Zhang/Hooker); NIH-NINDS
Funding Agency's Contracting/Grants Officer (name/address): Brenda Kibler, GM Specialist; kiblerb@ninds.nih.gov
Performance Period: 09/15/2013 – 08/31/2016 (NCE)
Funding Amount: $147,719
Brief Description of Project's Goals: We propose to use PET/MRI with a novel inflammatory tracer to study the association between inflammation, structural changes, and symptoms in patients with sciatica pain.
List of Specific Aims: Specific Aim 1: Establish a method for imaging lumbar spine neuraxial inflammation using MR-PET and [11C]PBR28 imaging technology in radicular pain patients. Specific Aim 2: Correlate the existence, location, and intensity of neuraxial inflammation, as revealed by MR-PET and [11C]PBR28 imaging, with MRI structural changes and clinical pain symptoms, including pain location, quality, and intensity at the disease baseline. Specific Aim 3: Assess the relationship between neuraxial inflammation and response to ESI by comparing the pre- and post ESI pain location, intensity, and functional assessment between groups of sciatica pain patients with or without neuraxial inflammation as revealed by MRPET [11C]PBR28 imaging.
Project Role: Co-Investigator
Overlap: None

Project Title: PET Imaging of Local Inflammation and Function in Ventilator Induced Lung Injury
Time Commitment: 3.24 Cal. Mos.
Supporting Agency: 5R01-HL086827-05 (Vidal Melo); NIH-NHLBI
Funding Agency's Contracting/Grants Officer (name/address): Dianna Jessee, GM Specialist; jessed@nhlbi.nih.gov
Performance Period: 01/10/2007 – 12/31/2013 (NCE)
Funding Amount: $279,029
Brief Description of Project's Goals: The long term goal of this research project is to elucidate the mechanisms producing acute lung injury (ALI) and to develop methods to investigate, prevent and treat this condition.
List of Specific Aims: Specific Aim 1: To validate Positron Emission Tomography (PET) measurements of in-vivo intrapulmonary neutrophil trafficking and activity against histopathological measurements of lung injury. Specific Aim 2: To use those PET measurements to test whether regional neutrophilic inflammation and deterioration of regional ventilation and perfusion result from either: a) heterogeneous mechanical stretch applied with 'safe' ventilator settings to normal and to endotoxin-primed lungs, or b) remote effects of excessive mechanical stretch applied to other regions of the lung. Specific Aim 3: To test whetehr regional lung perfusion, measured with PET, modulates regional neutrophilic inflammation during mechanical ventilation.
Project Role: PI
Overlap: None

Project Title: Intraoperative Protective Ventilation and Postoperative Pulmonary Complications
Time Commitment: 2.4 Cal. Mos.
Supporting Agency: 5R34-HL123438-03 (Vidal Melo); NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Sunshine Wilson, GM Specialist, wilsonsa2@mail.nih.gov
Performance Period: 07/15/2015 – 03/31/2019 (NCE)
Funding Amount: $24,973
Brief Description of Project's Goals: Our long-term goal is to develop and implement perioperative strategies to eliminate postoperative pulmonary complications.
List of Specific Aims: Specific Aim 1: To characterize usual-care practices for mechanical ventilation during abdominal surgery in major US academic centers. Specific Aim 2: To prospectively compare two methods to individualize PEEP settings in the operating room during abdominal surgery: (1) Maximization of respiratory compliance during a decremental PEEP titration, and (2) Prevention of negative end-expiratory transpulmonary pressures (Ptp). Specific Aim 3: To establish the processes required for the implementation of the full-scale multi-center clinical trial.
Project Role: PI
Overlap: None

Project Title: Regional Tidal Lung Strain and Neutrophilic Inflammation in Early Lung Injury
Time Commitment: 3.12 Cal. Mos.
Supporting Agency: 5R01-HL121228-04 (Vidal Melo); NIH-NHLBI
Funding Agency's Contracting/Grants Officer (name/address): Taryn Cobb, GM Specialist; cobbt@mail.nih.gov
Performance Period: 01/01/2014 – 04/30/2019
Funding Amount: $346,986
Brief Description of Project's Goals: We will study how inflammation is produced by regional lung strain during mechanical ventilation, and whether early inflammation is related to subsequent lung damage and dysfunction.
List of Specific Aims: Specific Aim 1: To assess the regional effects of tidal volumetric strain on pulmonary FDG kinetics, tissue neutrophilic inflammation, and neutrophil gene expression. Specific Aim 2: To ascertain the dependence of regional parenchymal damage, neutrophilic inflammation, and lung dysfunction at 24h of lung injury on earlier local cellular metabolic activity quantified with FDG-PET. If FDG uptake during early lung injury measures the initial neutrophilic inflammation triggered by injurious stimuli, then regions of increased uptake should display subsequent effects of that inflammation such as parenchymal damage and dysfunction. Specific Aim 3: Within the first 48h of mechanical ventilation in septic patients, to establish the relationship between pulmonary neutrophilic inflammation and both regional lung strain and the ensuing degree of lung dysfunction.
Project Role: PI
Overlap: None

Project Title: Preoperative Rehabilitation of Patients Undergoing Flung Resection Surgery
Time Commitment: no measurable effort required
Supporting Agency: MGH-DACCPM
Funding Agency's Contracting/Grants Officer (name/address): Maria Harlow, Administrative Director, MGH DACCPM Research Council; mharlow@partners.org
Performance Period: 06/01/2016 – 05/31/2018 (NCE)
Funding Amount: $173,913

Brief Description of Project's Goals: The goal of this study is to create a comprehensive regimen of preoperative and postoperative interventions that reduce postoperative pulmonary complications and improve high risk patient outcomes.
List of Specific Aims: Specific Aim 1: To establish that a short-term (3 weeks minimum) program of aerobic and strength training in high-risk patients scheduled to undergo curative lung resection can result in a meaningful increase in the 6 minute walk distance (6MWD), a measure associated with functional exercise capacity. Specific Aim 2: To determine if there is a difference in the incidence of postoperative pulmonary complications among those who participate in prehabilitation as compared to controls based on review of clinical outcomes. Specific Aim 3: To assess the changes in inflammatory state associated with a prehabilitation program through immunology assays, RNA sequencing and genetic analysis.
Project Role: PI
Overlap: None

CURRENT

Project Title: PET/CT-guided personalized mechanical ventilation to minimize ventilator-induced lung injury
Time Commitment: 3.12 Cal. Mos.
Supporting Agency: 2R01-HL121228-05 (Vidal Melo); NIH-NHLBI
Funding Agency's Contracting/Grants Officer (name/address): Lora Reineck, M.D., lora.reineck@nih.gov
Performance Period: 05/01/2019 – 04/30/2023
Funding Amount: $478,897
Brief Description of Project's Goals: We hypothesize that regional lung mechanical deterioration characterized by an increase in strain and aeration heterogeneity with current clinical ventilatory strategies produces changes in pulmonary blood volume conducive to endothelial injury, and composes the substrate for inflammation and early VILI in large heterogeneously inflated lungs. We will test this hypothesis with respiratory-gated PET/CT by using CT-derived lung strains and aeration to ascertain global mechanics measures best indicative of the positive end-expiratory pressure (PEEP) leading to homogenous stretch distributions in sheep.
List of Specific Aims: The specific aims of this project are to use respiratory-gated PET/CT to personalize positive end-expiratory pressure (PEEP) and assess its effect on: (a) strain deterioration, and the spatial relation of this deterioration with tidal capillary closure, endothelial damage, and lung injury in clinically relevant 48h sheep studies; and (b) local distributions of strain and aeration in septic patients.
Project Role: PI
Overlap: None

Project Title: 1/2: An Anesthesia-Centered Bundle to Reduce Postoperative Pulmonary Complications: The PRIME-AIR Study
Time Commitment: 3.86 Cal. Mos.
Supporting Agency: 1UG3-HL140177-01A1 (Vidal Melo); NIH-NHLBI
Funding Agency's Contracting/Grants Officer (name/address): Drs. Lora Reineck and James P. Kiley; lora.reineck@nih.gov, NIH-NHLBI
Performance Period: 12/01/2018 – 11/30/2023
Funding Amount: $938,351

Brief Description of Project's Goals: The goal of this randomized controlled trial is to test whether a new anesthetic-centered budle reduces the rates of PPCs after abdominal surgery, the field with the largest absolute number of those complications. If successful, this bundle could change clinical practice and have a substantial impact in reducing postoperative pulmonary morbidity.
List of Specific Aims: Specific Aim 1: To compare the number and severity of PPCs in patients receiving an individualized perioperative anesthesia-centered bundle to those in patients receiving usual anesthetic care during open abdominal surgery. Specific Aim 2: To assess the effect of the proposed bundle on plasma levels of lung injury biomarkers.
Project Role: Contact PI
Overlap: None

Project Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Time Commitment: 2.4 Cal. Mos.
Supporting Agency: W81XWH1810667 (Choi); Army Medical Research and Material Command
Funding Agency's Contracting/Grants Officer (name/address): Snyder, Sandy; sandy.j.snyder.ctr@mail.mil
Performance Period: 09/15/2018 – 09/14/2022
Funding Amount: $190,549 (MGH Year 1 direct)
Brief Description of Project's Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
List of Specific Aims: Specific Aim 1: To evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS. Specific Aim 2: To investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Project Role: Co-Investigator
Overlap: None

PENDING

Project Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Time Commitment: 2.4 Cal. Mos. in Years 2-4
Supporting Agency: NIH-NHLBI (Choi/Fredenburgh)
Funding Agency's Contracting/Grants Officer (name/address): Reineck, Lora A; lora.reineck@nih.gov
Performance Period: 07/01/2020 – 06/39/2024
Funding Amount: $348,291 direct costs year 1
Brief Description of Project's Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.
List of Specific Aims: Specific Aim 1: To evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm. Specific Aim 2: To examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.
Project Role: Co-Investigator
Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes

to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PREVIOUS/CURRENT/PENDING SUPPORT:

THOMPSON, B. TAYLOR

CURRENT

5R01HL119344-05 (Thompson) 01/01/2014-12/31/2019 0.60 CM
NIH/NHLBI $348,695
Contracting Officer: REINECK, LORA A. (lora.reineck@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952
Use of advanced imaging techniques to improve diagnostic methods for ARDS
Goals: This project will research modern advances in imaging and blood testing methods to improve techniques in diagnosing ARDS.
Specific Aims: SPECIFIC AIM 1: We will perform PET/CT imaging of critically ill patients to compare lung inflammation (18F-FDG) and pulmonary edema (H215O) in ARDS vs. heart failure, and compare these with a novel model using 18F-FDG data alone to quantify inflammation and edema. We hypothesize that PET/CT imaging will enable separation of subjects into diagnostic groups according to underlying pulmonary inflammation and edema. SPECIFIC AIM 2: We will test the relationship between lung inflammation and novel biomarker sST2. We hypothesize that plasma concentration of sST2 can be used as a surrogate for imaging to detect lung inflammation, and thus can enable diagnostic separation of subjects according to the presence of this process.
Role: PI
Overlap: None

5U01HL123009-04 (Schoenfeld) 04/01/2014-03/31/2021 4.80 CM
NIH/NHLBI $888,579
Contracting Officer: REINECK, LORA A. (lora.reineck@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952
CCC for NHLBI Prevention and Early Treatment of Acute Lung Injury PETAL Network
Goals: This proposal is a response to the RFA-HL-14-015 for the coordinating center of the Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. We propose to provide leadership in the design, analysis and conduct of the studies of the PETAL Network and to provide the infrastructure and communications that will create a cohesive and productive group.
Specific Aims: Aim 1: To collaborate on the development of innovative studies that will reduce ARDS morbidity and mortality by early treatment of patients with ARDS and by preventing ARDS in patients at risk. Aim 2: To plan and implement a program to collect patient samples to be used in studies of biomarkers to predict ARDS risk and response to therapies, understand ARDS pathogenesis, and suggest targeted therapies. Aim 3: To provide a state of the art electronic data capture system, ensure high quality data, measure and improve protocol compliance, and monitor and improve these activities at the sites. Aim 4: To create a cohesive network by organizing meetings and conference calls and creating a network identity through a website and newsletter. This will include a meeting of critical care experts to prioritize network studies. Aim 5: To initiate studies by assisting in development of an efficient Institutional Review Board process for the network and by facilitating development and approval and organizing timely protocol initiation and

drug distribution. Aim 6: To ensure patient safety by meticulous protocol development, novel adverse event reporting, and by providing a complete, easily readable report to the Data and Safety Monitoring Board and the FDA. Aim 7: To assist in the writing of manuscripts by providing logistics support and statistical analysis.
Role: Co-PI
Overlap: None

W81XWH1810667 (Choi) 09/15/2018-09/14/2022 1.20 CM
Army Medical Research and Material Command $190,549 (MGH Yr 1 direct)
Contracting Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Role: Co-Investigator/Co-Director of Data Coordinating Center
Overlap: None

5R35HL140026-02 (Calfee) 01/16/2018-02/28/2024 0.60 CM
NIH/NHLBI $12,464 (MGH only)
Contracting Officer: REINECK, LORA A. (lora.reineck@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952
Precision Medicine in the Acute Respiratory Distress Syndrome
Goals: To identify endotype-specific treatment responses and differences in endotype biology within ARDS.
Specific Aims: In Aim 1, we will test a practical, parsimonious model to identify ARDS endotypes in SAILS and ROSE, as well as in a more diverse ARDS cohort at UCSF. In Aim 2, we will identify specific differences in the biology of ARDS endotypes through analysis of novel candidate protein, lipid and metabolite biomarkers as well as high-throughput genomic sequencing, in the setting of the ROSE trial.
Role: Site PI
Overlap: None

5R01NS102190-02 (Westover) 04/01/2018-03/31/2023 0.60 CM
NIH/NINDS $490,931 (Yr 1 direct)
Contracting Officer: HE, JANET (hey@ninds.nih.gov), NINDS- Neuroscience Center, Division of Extramural Activities, 6001 Executive Boulevard Suite 3309, Bethesda, MD 20892
Investigation of Sleep in the Intensive Care Unit (ICU-SLEEP)
Goals: Investigation of Sleep in the Intensive Care Unit (ICU-SLEEP).
Specific Aims: Sleep deprivation is common and severe in critically ill patients cared for in intensive care units (ICUs), and is hypothesized to be a key modifiable risk factor for delirium and long-term cognitive disability. Dexmedetomidine reduces the incidence of delirium in ICU patients by unknown mechanisms. The specific aims of this project are to determine whether

dexmedetomidine reduces delirium by improving sleep, whether bolus dosing vs continuous infusion is better, and the relationship of sleep quality to long-term cognitive outcomes.
Role: Co-Investigator
Overlap: None

PREVIOUS

5R34HL123438-03 (Vidal Melo) 07/15/2015-03/31/2019 0.36 CM
NIH/NHLBI $229,933
Contracting Officer: REINECK, LORA A. (lora.reineck@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952
Intraoperative Protective Ventilation And Postoperative Pulmonary Complications
Goals: Our long-term goal is to develop and implement perioperative strategies to eliminate postoperative pulmonary complications (PPCs). Whereas PPCs are as significant and lethal as cardiac complications, research in the field has received much less attention, and strategies to minimize PPCs are regrettably limited.
Specific Aims: Aim 1. To characterize usual-care practices for mechanical ventilation during abdominal surgery in major US academic centers. Aim 2. To prospectively compare two methods to individualize PEEP settings in the operating room during abdominal surgery: (1) maximization of lung compliance during a decremental PEEP titration, and (2) prevention of negative end-expiratory transpulmonary pressures by measuring esophageal balloon pressures. With these Aims, we will determine the control (Aim 1) and intervention (Aim 2) ventilatory settings for the full-scale trial. Aim 3. To establish the processes required for the implementation of the full- scale multi-center clinical trial. At the conclusion of these aims, we will have the necessary and sufficient data to launch a multicenter clinical trial to establish the effect of optimal PEEP settings to prevent PPCs after abdominal surgery. Accordingly, our project could result in a major change in clinical practice and paradigm on intraoperative mechanical ventilation.
Role: Co-Investigator
Overlap: None

5P01HL108801-05 (Perrella) 08/15/2011-06/30/2016 0.60 CM
BWH/NIH/NHLBI $24,190 (MGH only)
Contracting Officer: HARABIN, ANDREA L (andrea.harabin@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952
Core B-Clinical Studies Coordinator Care
Carbon Monoxide: Novel Opportunities for Therapy
Goals: This study seeks to test the hypothesis that carbon monoxide can provide tissue protective effects in sepsis and acute lung injury by preserving cellular homeostasis and promoting bacterial clearance.
Specific Aims: Aim 1: To identify patients with the systemic inflammatory response syndrome (SIRS), sepsis, and sepsis-induced acute lung injury (ALI); to collect and store plasma, RNA, and primary cells from subjects in a clinical biorepository; and to provide biostatistical support for Projects 1-4 for the analysis and interpretation of studies performed using these specimens. Aim 2: To serve as the DCC for the Phase 1 first-in-ALI safety study for inhaled CO in sepsis induced ALI in Project 1 and proof-of-concept study with collection of muscle biopsies after inhaled CO in Project 2.

Role: Core B PI
Overlap: None

5R01HL060710-13 (Christiani) 08/15/2012-05/31/2016 1.20 CM
HSPH/NIH/NHLBI $110,870 (sub-only)
Contracting Officer: HARABIN, ANDREA L (andrea.harabin@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952
Molecular Epidemiology of ARDS
Goals: To examine the association between specific polymorphisms for specific inflammatory responses and for surfactant protein and their potential association with increased susceptibility to ARDS.
Specific Aims: In Specific Aim 1, we will conduct whole exome sequencing on 100 ARDS cases and 100 matched controls to define target regions by integrating analysis of whole exome sequencing data with candidate genetic loci discovered in the previous cycle, as well as the current GWAS. With our collaborator, Dr. Mark Wurfel of University of Washington, we will also analyze available eQTL data to evaluate the functional relevance of the target regions. In Specific Aim 2, we will design a molecular inversion probe (MIP) panel for resequencing promoter/exons/miRNA/regulatory elements within the target regions defined in Aim 1; identify all variations using MIP capture coupled with deep NextGen sequencing and define candidate genes by evaluating the associations of functional rare/common variations with ARDS susceptibility and outcomes using variation aggregation methods. In Specific Aim 3, we will replicate the top-ranked genes by NextGen sequencing in a large collaborating external population with a similar study design.
Role: Site PI (Removed effort 05/31/16)
Overlap: None

5U01HL108713-03 (Matthay) 07/01/2013-06/30/2016 1.20 CM
UCSF/NIH/NHLBI $67,458 (sub-only)
Contracting Officer: HARABIN, ANDREA L (andrea.harabin@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952
Human Mesenchymal Stem Cells for the Treatment of Acute Lung Injury
Goals: This clinical trial will test the potential therapeutic value of cell-based therapy with bone marrow derived mesenchymal stem cells from normal adults (age 18-30) as a novel therapy to reduce mortality in critically ill patients with acute lung injury and acute respiratory failure.
Specific Aims: Hypothesis 1: Compared to placebo treatment, human MSC will reduce the severity of ALI as quantified by the 4-point composite ALI score. Hypothesis 2: Compared to placebo treatment, human MSC treatment will reduce non-pulmonary organ failures as measured by the Brussels Organ Score. Hypothesis 3: Compared to placebo treatment, human MSC will have an acceptable safety profile in patients with ALI. We are also proposing two ancillary studies, both of which will use samples of plasma and bronchoalveolar lavage fluid (BALF) from patients in the clinical trial to provide mechanistic insights into how human MSC reduce lung injury and non-pulmonary organ failure.
Role: Site PI
Overlap: None

PENDING

NIH/NHLBI (Choi) 07/01/2020-06/39/2024 0.60 CM

$348,291 direct costs year 1

Contracting Officer: REINECK, LORA A. (lora.reineck@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952

A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS

Goals: The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.

Specific Aims: The specific aims of this project are 1) to evaluate the safety and accuracy of a Coburn-Forster-Kane (CFK) equation-based personalized iCO dosing algorithm; and 2) to examine the impact of precision-based iCO dosing on functional biological signatures in patients with sepsis-induced ARDS.

Role: Co-Investigator/Co-Director of Clinical Coordinating Center

Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PREVIOUS/CURRENT/PENDING SUPPORT:

HESS, DEAN R.

PREVIOUS:
Title: Carbon Monoxide: Novel Opportunities for Therapy (5P01HL108801-05)
Effort: 1.2 Calendar Months (Core D)
Supporting Agency: NIH/NHLBI
Grants Officer: Harabin, Andrea L. (andrea.harabin@nih.gov)
Performance Period: 8/15/2011 – 6/30/2017 (No Cost Extension)
Funding Amount: $176,712 (Core D) direct costs per year (No Cost Extension)
Project Goals: The major goal of this study is to investigate carbon monoxide as a novel therapy for sepsis and ARDS.
Specific Aims: The specific aims of this project are 1) to elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection; 2) to identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI; and 3) to provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI in Cycle II of the translational PPG program.
Overlap: There is no overlap.

Title: Physiologic Profiling of SGC Genetic Variants (4R01HL113933-04)
Effort: 1.2 Calendar Months
Supporting Agency: NIH/NHLBI
Grants Officer: Youngsuk Oh (yoh@mail.nih.gov)
Performance Period: 8/5/2013 – 6/30/2017
Funding Amount: $ 323,356 direct costs per year
Project Goals: The overall goal of the proposed research program is to ascertain whether the GUCY1A3/GUCY1B3 genetic variant associated with blood pressure (or a closely linked variant) modulates expression of soluble guanylate cyclase alpha1 and/or beta1 subunits.
Specific Aims: In Aim 1, we seek to establish whether the association of BP with the SNP at the GUCY1A3/GUCY1B3 locus is likely to be determined by a difference in sGC activity. In Aim 2, genetic variants will be introduced into bacterial artificial chromosomes containing the human GUCY1A3/GUCY1B3 locus.
Overlap: There is no overlap.

CURRENT:
Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)
Effort: 50 hours per year (Consultant)
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)
Performance Period: 09/15/18 – 09/14/22
Funding Amount: $190,549 direct costs year 1 (MGH)
Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.

Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: There is no overlap.

PENDING:
None.

PREVIOUS/CURRENT/PENDING SUPPORT:

NOELLE SAILLANT

PRIOR SUPPORT
R01HL119248-04 (De, Survranu) 08/08/2017-03/30/2019 0.06 CM
Development and Validation of a Virtual Skill Trainer (VAST)
Subaward No. A12577 $12,716
NIH-NHLBI
Program Official: Punturieri, Antonello, Division of Lung Diseases, National Heart, Lung and Blood Institute, punturieria@nhlbi.nih.gov, Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952
Goals: To develop a virtual reality cricothyroidotomy trainer for medical education.
Specific Aims: (SA1) Design and develop the Virtual Airway Skill Trainer (VAST) platform. Specifically, we will develop (1) physics-based computational models of human anatomy based upon in vivo experimental studies; (2) an immersive 3D high definition (HD) head mounted display (HMD) system to represent the clinical environment (OR/ICU/ED); and (3) an innovative bi-manual force feedback hardware interface with tactile matrix gloves that allows representation of various patient anatomies associated with the difficult airway. (SA 2) Develop simulation scenarios for endotracheal intubation (ETI) and cricothyrotomy (CCT) procedures within the VAST by integrating the computational models and experimental data generated in SA1.

ACTIVE
W81XWH1810667 (Choi, Augustine) 09/15/2018-09/14/2022 0.24 CM
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
$$190,549 direct costs year 1 (MGH)
Army Medical Research and Material Command
Grants Officer: Snyder, Sandy, sandy.j.snyder.ctr@mail.mil
Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.
Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

PENDING
None

OVERLAP
None

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Not applicable.

QUAD CHARTS:

Not applicable.

9. APPENDICES

See enclosed Award Chart.

PR171025: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of Acute Respiratory Distress Syndrome (ARDS)

PI: Augustine M.K. Choi, M.D, Weill Medical College of Cornell University, NY **Budget:** $8,914,310

Topic Area: Acute Lung Injury **Mechanism:** FY17 Peer Reviewed Medical Research Program Clinical Trial Award

Research Area(s): 0801, 0403 **Award Status:** 15 September 2018 – 14 September 2022

Study Goals:

The overall goal is to conduct a randomized, placebo-controlled Phase II study of low dose inhaled carbon monoxide (iCO) for the treatment of acute respiratory distress syndrome (ARDS).

Specific Aims:

Specific Aim 1: To evaluate the safety, tolerability, and efficacy of low dose inhaled CO (iCO) in patients with ARDS. Hypothesis: Low dose iCO will be safe and well-tolerated and will reduce the severity of lung injury and nonpulmonary organ failure in ARDS patients. We will conduct a Phase II randomized, double-blind, placebo-controlled trial of low dose iCO in mechanically ventilated patients with ARDS. We will enroll 100 adult patients with ARDS (based on 85% power to detect a difference in lung injury score [LIS]) and randomize subjects to iCO or placebo (medical grade air) treatment with a 1:1 randomization scheme.

Specific Aim 2: To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS. Hypothesis: Low dose iCO will reduce mitochondrial dysfunction, attenuate inflammasome activation, and promote resolution of inflammation in ARDS patients. We will measure plasma levels of mitochondrial DNA, autophagy markers, inflammasome components, and lipid mediators in subjects pre- and post-treatment with iCO or placebo. We will determine whether CO modulates these novel pathways and evaluate if these candidate biomarkers correlate with clinical efficacy endpoints in ARDS patients in the Phase II trial.

Key Accomplishments and Outcomes:

Publications: None to date

Patents: None to date

Funding Obtained: None to date