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

PRINCIPAL INVESTIGATORS: Jeremy Weingarten, M.D.

CONTRACTING ORGANIZATION: Weill Medical College of Cornell University

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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. Seven sites have received approval from the USAMRMC Office of Research Protections (ORP) Human Research Protection Office (HRPO). Seven sites are activated for enrollment and are currently screening. Four subjects have been enrolled to date.

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 32 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 3 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 32 adult patients with ARDS (based on 80% power to detect a difference in mtDNA from baseline to day 5 between treatment arms) 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
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
-Subtask 2: Facilitate and Coordinate with Sites for hiring, training, supervision and fidelity checks as needed for attrition- Months 8-48
We have completed 100% of Subtask 1, Major Task 2. We have completed 100% of Subtask 2, Major Task 2.

Major Task 3: Prepare Study Related Documents, Equipment, and Procedures- Months 1-4
We have completed 100% of Major Task 3.

Major Task 4: Participant Recruitment, Therapy, Participant Evaluation- Months 4-46
Screening and recruitment are being conducted in the intensive care units (ICUs) at 7 participating sites. Four subjects have been enrolled to date and were treated with the study drug. Two additional sites (New York-Presbyterian Brooklyn Methodist, Duke Regional Hospital) were added to enhance enrollment. New York-Presbyterian Brooklyn Methodist was activated on 11/17/2020 and Duke Regional Hospital was activated as a new site on 6/11/2021. Washington University was also added as a site for enrollment on 3/3/2022, but the DSMB halted enrollment on 5/24/22 due to low study enrollment.

Major Task 5: Biomarker Assays and Statistical Analysis- Months 6-50
Work has not begun on Major Task 5. We just received approval for a NCE to embark upon this work in the coming period.

What was accomplished under these goals?

Major Task 1: Prepare CO in ARDS Protocol for Implementation

- 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.
- 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 7 participating sites.
- HRPO approval has been obtained for 7 sites.

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 University Hospital	1/24/2019	7/29/2019

Site	Initial IRB approval	HRPO Approval
Durham VA	3/12/2019	7/29/2019
NYPBMH	2/26/2020	06/24/2020
Duke Regional Hospital	7/2/2020	11/24/2021
Washington University	1/11/2022	3/3/2022

- During this reporting period, Protocol v.8.0, 9.0, 10.0 and halting of enrollment was approved by all site local IRBs after the DSMB halted enrollment on 5/24/2022.

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

- This Subtask was completed during the first year of the project. Ongoing trainings are conducted as needed to train new study staff and to refresh current staff.
- Since the last Annual Report, Washington University was added as a site, and all sites underwent training on protocol versions 8-10 until study enrollment was halted by the DSMB on 5/24/2022.

Major Task 2: Coordinate Study Staff for Clinical Trial, Subtask 2: Facilitate and Coordinate with Sites for hiring, training, supervision and fidelity checks as needed for attrition

- This Subtask has been completed.

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

- Major Task 3 has been completed.

Major Task 4: Participant Recruitment, Therapy, Participant Evaluation

- 4 subjects in total were enrolled, with no new subjects enrolled since the prior report, and as above, enrollment was halted on 5/24/2022 by the DSMB.

- A total of 1451 intubated patient records were reviewed across all sites. Three hundred participants met inclusion criteria. Of the participants that met inclusion criteria, 4 participants were enrolled and 296 participants were excluded.

Site	Activation Date	Pre-screened subjects	Met inclusion criteria	Had an exclusion	Enrolled
BWH	6/24/2019	**417**	**60**	**58**	**2**
WCM	7/1/2019	**385**	**91**	**91**	**0**
MGH	8/1/2019	**235**	**63**	**63**	**0**
Duke University Hospital	9/20/2019	**196**	**54**	**53**	**1**
Durham VA	9/20/2019	**11**	**3**	**3**	**0**

Site	Activation Date	Pre-screened subjects	Met inclusion criteria	Had an exclusion	Enrolled
NY-Presbyterian Brooklyn Methodist	11/17/2020	**154**	**22**	**21**	**1**
Duke Regional Hospital	6/11/2021	**53**	**7**	**7**	**0**
Washington University	Not activated	**0**	**0**	**0**	**0**
Total		**1451**	**300**	**296**	**4**

The most common reason for exclusions* were:

- Severe hypoxemia (n=84)
  - Protocol versions 1-6: Severe hypoxemia defined as SpO2 < 95 or PaO2 < 80 on FiO2 ≥ 0.8 (n=41)
  - Protocol versions 7-10: Severe hypoxemia defined as SpO2 <95 or PaO2 <90 on FiO2 >= 0.9 (n=43)
- Stroke (n=56)
  - Protocol versions 1 – 6: Stroke (ischemic or hemorrhagic) or anoxic/hypoxic brain injury or traumatic brain injury (TBI) within the prior 3 months (n=35)
  - Protocol version 7: Stroke (ischemic or hemorrhagic) within the prior 1-month, cardiac arrest requiring CPR within the prior 72 hours, or inability to assess mental status following cardiac arrest (n=21)
- Moribund patient not expected to survive 24 hours (n=43)
- Out of window for ARDS onset criteria (n=35)
  - Protocol versions 1 – 4: Greater than 120 hours since ARDS onset (n=23)
  - Protocol versions 5 – 7: Greater than 168 hours since ARDS onset (n=12)
- Low hemoglobin (n=28)
  - Protocol versions 1- 6: Hemoglobin < 7.5 g/dL or hemoglobin < 8 g/dL and actively bleeding (n=22)
  - Protocol versions 7-10: Hemoglobin < 7.0 g/dl (n=6)
- Use of extracorporeal membrane oxygenation (ECMO) (n=28)
- Concomitant use of inhaled pulmonary vasodilator therapy (n=39)
- Acute myocardial infarction or acute coronary syndrome within the last 90 days (n=30)
- Patient, surrogate, or physician not committed to full support (n=18)
- Diffuse alveolar hemorrhage from vasculitis (n=17)

* Please not that some participants met more than one exclusion criteria.

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 have recently obtained a NCE to focus on analysis of biomarkers regulated by CO exposure.
- We will obtain IRB approval at all sites and HARPO approval to include additional CO-treated subjects from a similar Phase 1a study in these analyses.
- We will perform elegant and expansive biological assays on enrolled subjects pre- and post-CO exposure to identify relevant pathways that could present novel therapeutic targets.
- We will expand clinical analysis of CO administration and correlate physiologic parameters with biologic endpoints.

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

Due to low enrollment, the DSMB halted study enrollment one 5/24/2022. We obtained approval for a NCE to further enhance biologic analysis of the samples to gain further knowledge related to the potential benefits of CO administration in ARDS.

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

As above, despite extensive efforts, the COVID pandemic and associated staff shortages and logistical issues presented significant limitations to patient enrollment. The DSMB therefore halted enrollment on 5/24/2022. We have substantially expanded the planned biologic analyses to gain important insights from the enrolled subjects that will be of critical importance to ARDS therapeutics.

Changes that had a significant impact on expenditures

As above, halting enrollment permitted remaining budget to be applied to a NCE.

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?

New York-Presbyterian Brooklyn Methodist Hospital

Name:	**Jeremy Weingarten**
Project Role:	Principal Investigator (contact)
eRA Commons ID	78411852
Nearest person month worked:	3

Contribution to Project: Dr. Weingarten has overseen the IRB submission and approval at Brooklyn Methodist Hospital, HRPO submission, and is coordinating and facilitating the trial start-up activities at Brooklyn Methodist Hospital including preparation of trial-related equipment. Dr. Weingarten will oversee screening and enrollment of subjects at Brooklyn Methodist Hospital, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data. Effective 8//1/21 Dr. Weingarten is overseeing the research proposal and the overall planning and execution of the clinical trial grant.

Name: **Liziamma George**
Project Role: Site PI
eRA Commons ID
Nearest person month worked: 0.6
Contribution to Project: Dr. George oversees screening and enrollment of subjects at Brooklyn Methodist Hospital, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data.

Name: **Mayel Gharanei**
Project Role: Research Coordinator
eRA Commons ID
Nearest person month worked: 0.6
Contribution to Project: Dr. Gharanei has assisted with the trial start-up activities at New York-Presbyterian Brooklyn Methodist Hospital including assisting with the IRB submission, obtaining trial-related equipment and supplies, and communicating with the DCC in preparation for trial implementation. Ms. Edwards is responsible for screening the ICUs for potential participants meeting study eligibility criteria at Brooklyn Methodist Hospital and entry of subject data into the study database.

Weill Cornell Medicine

Name: **Augustine Choi**
Project Role: Principal Investigator
eRA Commons ID: CHOIAM
Nearest person month worked: 0.6
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: 0.6
Contribution to Project: Dr. Plataki has overseen the IRB submission and approval at Weill Cornell, has helped coordinate the 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, and will oversee 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 implementing screening in the trauma and burn ICUs.

Name: **Luis Gomez-Escobar**
Project Role: Research Coordinator
eRA Commons ID
Nearest person month worked: 12
Contribution to Project: Dr. Gomez-Escobar is responsible for study screening, subject enrollment, and management of clinical data, study records, and regulatory processes at Weill Cornell.

Name: **Michelle LoPiccolo**
Project Role: Project Administrative Coordinator
eRA Commons ID
Nearest person month worked: 4.2
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: **Rebecca Baron**
Project Role: Site PI/ Co-Investigator
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 with Dr. Fredenburgh and 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 is independently evaluating all safety and monitoring data from the trial on a quarterly basis.

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 is serving as a blinded investigator to adjudicate adverse events (AEs) at BWH. He reviews all AEs and assesses 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 is assisting with quarterly reporting to the DSMB and will oversee data analysis of the study endpoints.

Name: **Katherin Zambrano Vera**
Project Role: Project Manager
eRA Commons ID:
Nearest person month worked: 12
Contribution to Project: Dr. Zambrano Vera is overseeing regulatory submissions and reporting requirements under the supervision of Dr. Fredenburgh. She is working closely with the PIs and research coordinators at each site in the conduct of the trial to ensure that all clinical study procedures are performed in accordance with Good Clinical Practice (GCP) standards. Dr. Zambrano Vera is responsible for daily screening in the ICUs at BWH, subject enrollment, subject data collection, entry of data into the clinical trial database in StudyTRAX, and identification of AEs in conjunction with Dr. Fredenburgh.

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: **Oluwaseun Johnson-Akeju**
Project Role: Site PI
eRA Commons ID: OJOHNSON-AK
Nearest person month worked: 1.52
Contribution to Project: Dr. Johnson-Akeju supervised the trial management team at MGH including preparations associated with the research coordinator and respiratory therapists.

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: 0.19
Contribution to Project: Dr. Saillant participated in preparing the conduct of the project in the trauma and burn ICUs at MGH.

Name: **Diana Barragan Bradford**
Project Role: Project Coordinator
eRA Commons ID: DIANABB
Nearest person month worked: 0.23
Contribution to Project: Dr. Barragan Bradford assisted Dr. Johnson-Akeju with day-to-day oversite of the trial management team at MGH. Dr. Barragan Bradford 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: **Anthony Khoudary**
Project Role: Clinical Research Coordinator I
eRA Commons ID:
Nearest person month worked: 1.75
Contribution to Project: Mr. Khoudary participated in necessary training activities and was responsible for screening subjects for enrollment in the study at MGH.

Duke University, Duke Regional Hospital, and 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, Duke Regional Hospital, and the Durham VA Hospital. Dr. Welty-Wolf's effort has been devoted to supervision of study start-up, obtaining IRB approval, and subaward administration at both sites. Dr. Welty-Wolf is overseeing screening and enrollment of subjects, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data.

Name: **Cory 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. Dr. Vatsaas' effort has been assisting with study start-up and screening in the surgical ICUs.

Name: **John Davies**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 4.8
Contribution to Project: Mr. Davies is a Registered Respiratory Therapist and will supervise CO study gas administration. He is responsible for CO device calibration, performance testing, and continuous maintenance of study equipment. He is responsible for education and training of respiratory therapists across all study sites in equipment use and calibration and for study drug administration. Mr. Davies is providing on call support to all sites for any issues that arise with study drug administration during the conduct of the study. Mr. Davies has assisted with study start-up, including equipment preparation and education and training of respiratory therapists in CO administration in preparation for study subject enrollment.

Name: **Brittany McDowell**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 2.1
Contribution to Project: Ms. McDowell is responsible for study screening, subject enrollment, and management of clinical data, study records, and regulatory processes at Duke University Hospital and Duke Regional Hospital.

Name: **Lingye Chen**
Project Role: Co-Investigator
eRA Commons ID: LINGYE.CHEN
Nearest person month worked: 2.4
Contribution to Project: Dr. Chen will assist with subject enrollment and data collection at Duke University Hospital, and with study drug administration across all sites. She has experience with ICU and COVID Biorepository management and biorepository-based research collaborations.

Name: **Eugene Friedman**
Project Role: Co-Investigator
eRA Commons ID: YF1234
Nearest person month worked: 2.4
Contribution to Project: Dr. Friedman is responsible for recruitment at Duke Regional Hospital and will assist with data collection and study drug administration across all sites. He has experience with clinical trial implementation in hospitalized patients with COVID pneumonia.

Name: **Wendy Curry**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 1.4
Contribution to Project: Ms. Curry is responsible for study screening, subject enrollment, and management of clinical data, study records, and regulatory processes at Duke University Hospital and Duke Regional Hospital.

Washington University

Name: **Bryan Kraft**
Project Role: Site PI
eRA Commons ID: bryankraft
Nearest person month worked: 1.4
Contribution to Project: Dr. Kraft oversees all study conduct and procedures including patient screening, enrollment, treatment, monitoring, and reporting.

Name: **Daniel Reynolds**
Project Role: Co-Investigator
eRA Commons ID: REYNOLDSD
Nearest person month worked: 0.6
Contribution to Project: Dr. Reynolds assists as a Co-investigator with study procedures, including patient screening, enrollment, treatment, monitoring, and reporting.

Name: **Olagoke Osanyinlusi**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 12.0
Contribution to Project: Mr. Osanyinlusi is responsible for study screening, subject enrollment, and management of clinical data, study records, and regulatory processes at Washington University.

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:

WEINGARTEN, JEREMY

ACTIVE GRANTS

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
W81XWH1810667 (J. Weingarten/A. Choi)
Effort: 3 Calendar Months (contact PI)
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)
Performance Period: 02/14/2020 – 09/14/2023
Funding Amount:
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: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
R33HL153011 (A. Choi/ R. Baron - Multi-PI)
Effort: 1.2 Calendar Months (site PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Zhou, Guofei (guofei.zhou@nih.gov)
Performance Period: 09/01/2022-08/31/2025
Funding Amount:
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: This Phase Ib study is distinct and has no scientific or budgetary overlap with the Phase II trial supported by the Department of Defense. The Phase Ib study will 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).

PENDING GRANTS
NONE

PREVIOUS SUPPORT FOR GRANTS ACTIVE WITHIN THE PAST 5 YEARS

Title: Beta-Blockers for the Prevention of Acute Exacerbations of COPD
W81XWH1510705 (J. Weingarten)
Effort: No measurable effort, capitated patient reimbursement costs, (PI)
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Susan M. Dellinger susan.m.dellinger.civ@mail.mil

Performance Period: 10/01/2016 – 09/30/2019
Funding Amount:
Project Goals: A safety and efficacy study of once-daily metoprolol succinate versus placebo in COPD patients at risk for acute exacerbation to determine the effect of beta-blockade on lung function, dyspnea, quality of life, exercise tolerance and exacerbation risk.
Specific Aims: Primary: To determine the effect of once daily metoprolol succinate compared with placebo on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and who do not have absolute indications for beta-blocker therapy.
Overlap: There is no overlap.

Title: Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection
Effort: 0.6 Calendar Months (PI)
Supporting Agency: Gilead Sciences, Inc
Grants Officer: Jennifer Parulis
Performance Period: 04/24/2020 –9/23/2020
Funding Amount: No funding
Project Goals: To provide expanded access of RDV for the treatment of SARS-CoV2 infection
The secondary objective of this study is: To evaluate the safety of RDV with respect to incidence of treatment-emergent AEs
Specific Aims: The primary endpoint of this study is: The incidence rate of treatment-emergent AEs
Overlap: There is no overlap.

Title: Evaluation of fluid volume in patients with sepsis and refractory hypotension (FRESH)
Effort: 0.6 Calendar Months (site PI)
Supporting Agency: Cheetah Medical
Grants Officer: Jennifer Sahatjian
Performance Period: 11/30/2016-8/25/2020
Funding Amount:
Project Goals: The major goal of this study is to assess outcomes, based on a dynamic assessment of fluid responsiveness in septic patients with refractory hypotension in an ICU setting.
Specific Aims: This clinical trial aims to assess the mean difference in fluid balance and associated patient outcomes, based on a dynamic assessment of fluid responsiveness via the Noninvasive Starling™ SV device in septic patients with refractory hypotension in an ICU setting.
Overlap: There is no overlap.

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

ACTIVE GRANTS

W81XWH1810667 (J. Weingarten/ A. Choi – Multi-PI) 09/15/2018-09/14/2023 NCE 0.6 calendar months
Department of Defense
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Role: Co-PI
Direct Costs:
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, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: None

R01 HL055330 (A. Choi/M. Choi – Multi-PI) 04/01/2018-03/31/2023 NCE 0.12 calendar months
NIH/NHLBI
Inflammasomes: Regulation and Function in Acute Lung Injury
Direct Costs:
Role: Co-PI
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

P01 HL114501 (Choi) 06/10/2021-04/30/2026 0.45012 CM Core A/1.8012 CM 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: (Proj 1), (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-β1 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-13Rα2 glycosylation and epigenetic modifications of IL-13Rα2 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

R33HL153011 (A. Choi/ R. Baron) 09/01/2022 – 08/31/2025 1.8012 calendar months
NIH/NHLBI
A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Role: PI
Name and address of Contracting/Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Direct Costs:
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: This Phase Ib study is distinct and has no scientific or budgetary overlap with the Phase II trial supported by the Department of Defense. The Phase Ib study will 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).

T32 HL134629-01A1 (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
None

COMPLETED SUPPORT

R01 HL133801 (M. Choi/ A. Choi - Multi-PI) 08/01/2017-07/31/2022 0.0912 calendar months
NIH/NHLBI
Novel role of RIPK3-dependent necroptosis pathway in lung and kidney fibrosis
Direct Costs:
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

GRL Phase II (Yoon) 03/01/2019-06/60/2022 0.12 calendar months

National Research Foundation of Korea

Development of predictive biomarkers for refractory allergic airway disease

Role: PI

Direct Costs:

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

R01 HL132198 (A. Choi/M. Choi - Multi-PI) 01/01/2017-12/31/2021 0.12 calendar months

NIH/NHLBI

Metabolic dysfunction regulates mitophagy-dependent necroptosis in COPD

Direct Costs:

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 HL060234 (M. Choi/ A.M.K Choi - Multi-PI) 03/14/2014-01/31/2020 0.12 calendar months

NIH/NHLBI

Heme Oxygenase-1/Carbon Monoxide in Lung Vascular Injury

Direct Costs:

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

PREVIOUS/CURRENT/PENDING SUPPORT:

MARIA PLATAKI, MD, PhD

ACTIVE GRANTS

W81XWH1810667 (J. Weingarten/A. Choi) 09/15/2018 – 09/14/2023 (NCE) 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:
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, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: None

K08 HL157728 (Plataki) 01/15/2022-12/31/2026 9.0 calendar months
NIH/NHLBI
Impact of Diet Induced Obesity on Acute Lung Injury
Role: Principal Investigator
Direct Costs:
Name and address of Contracting/Grants Officer: Tracee Foster, email: gilchrit@mail.nih.gov
Goals: The goal of this project is to characterize the regulation of high fat diet associated pathways in the lung and their role in the pathogenesis of acute lung injury.
Specific Aims: Aim 1. To investigate the role of FA utilization in the pathogenesis of experimental obesity induced acute lung injury.
Aim 2. To delineate the association between FASN regulation, mitochondrial dynamics and AEC2 dysfunction in acute lung injury with high fat diet.
Aim 3. To characterize dysregulated metabolic pathways based on body mass index (BMI) in patients with ARDS.

R33HL153011 (A. Choi/ R. Baron) 09/01/2022 – 08/31/2025 0.6 calendar months
A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Role: Co-Investigator
Direct Costs:
Name and address of Contracting/Grants Officer: Zhou, Guofei (guofei.zhou@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: This 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 Phase Ib will 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).

PENDING GRANTS
None
COMPLETED GRANTS
R01HL060234 (M. Choi/A. Choi) 03/14/2014 – 01/31/2020 (NCE) 0.118 calendar months
NIH/NHLBI
Heme Oxygenase-1/Carbon Monoxide in Lung Vascular Injury
Role: Co-Investigator
Direct Costs:
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

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:
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
Participation ended Jan 2022

PREVIOUS/CURRENT/PENDING SUPPORT:

MARY E. CHOI, MD

ACTIVE GRANTS

W81XWH1810667 (J. Weingarten/ A. Choi – Multi-PI) 09/15/2018 – 09/14/2023 NCE 3.0 calendar months
Department of Defense
A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Role: Co-Investigator
Direct Costs:
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, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).
Overlap: None

R33HL153011 (A. Choi/ R. Baron) 09/01/2022 – 08/31/2025 1.2 calendar months
NIH/NHLBI
A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Role: Co-Investigator
Name and address of Contracting/Grants Officer: Lora Reineck (lora.reineck@nih.gov)
Direct Costs:
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: This Phase Ib study is distinct and has no scientific or budgetary overlap with the Phase II trial supported by the Department of Defense. The Phase Ib study will 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).

P01HL114501 (A. Choi) 09/06/2013-04/30/2026 1.2 calendar months
NIH/NHLBI
Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers
Role: Co-Investigator
Direct Costs: (Project 1)
Name and address of Contracting/Grants Officer: Dr. David Goff, Division of Lung Diseases; National Heart, Lung and Blood Institute 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.

Overlap

None

R01HL055330 (A. Choi/M. Choi) 04/01/2018 – 03/31/2023 NCE 3.0 calendar months

NIH/NHLBI

Inflammasomes: Regulation and Function in Acute Lung Injury

Role: Co-PI (Contact)

Direct Costs:

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

R01DK113088-5 (L. Gudas) 12/04/2017 – 7/31/2026 0.45 calendar months

NIH/NIDDK

Gene Nutrient Interactions in Kidney Function

Role: Collaborator

Direct Costs:

Name and address of Contracting/Grants Officer: Krystle Nicholson, Grants Management Specialist, National Institute of Diabetes and Digestive Kidney Diseases; nicholsonk@niddk.nih.gov; 301-594-8860 10.

Goals: We anticipate that retinoic acid receptor (RAR) β agonists will be useful in diminishing the severity of nephropathy in several murine models of chronic kidney disease. Data from this study could lead to new molecular targets for the treatment of various kidney disorders.

Specific Aims: Aim 1: Because we have evidence that a selective RARβ2 agonist has a therapeutic impact on the development of CKD in one mouse model, we propose to test the efficacy of this RARβ2 agonist in two additional CKD models, potentially creating a rationale to use it as a lead compound for treatment of CKD and to define its gene targets. **Aim 2:** Our genetic approach to study the micronutrient vitamin A has been fruitful and has generated several potentially useful models of various types of CKD. Furthermore, our results suggest the interaction of the kidney with other organ systems is different in different mouse models. Thus, we propose to evaluate the actions of the retinoic acid receptors α, β, and γ in specific cell types in the kidney and test the usefulness of these novel models of CKD.

Overlap

None

PENDING GRANTS
None

COMPLETED GRANTS
R01HL133801 (M. Choi/A. Choi) 08/01/2017 – 07/31/2022 3.0 calendar months
NIH/NHLBI
Novel role of RIPK3-dependent necroptosis pathway in lung and kidney fibrosis
Role: Co-PI (Contact)
Direct Costs:
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 – 12/31/2021 2.4 calendar months
NIH/NHLBI
Metabolic dysfunction regulates mitophagy-dependent necroptosis in COPD
Role: Co-PI
Direct Costs:
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 1.38 calendar months
NIH/NHLBI

Heme Oxygenase-1/Carbon Monoxide in Lung Vascular Injury
Role: Co-PI (Contact)
Direct Costs:
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

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:
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

PREVIOUS/CURRENT/PENDING SUPPORT:

BARON, REBECCA

PREVIOUS SUPPORT

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 – 02/28/2021
Funding Amount:
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: 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:
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

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: (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: Phase 2 Study of Safety, Tolerability, and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease
Effort: 1.2 calendar months
Supporting Agency: Investigator Initiated Clinical Trial, Genentech / Roche (Goldberg, PI; Baron, medical monitor)
Performance Period: 04/01/2016 – 03/31/2021

Funding Amount: total cost
Project Goals: 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

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 – 5/31/2021 (NCE)
Funding Amount:
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: CCC for NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Network (CORAL Study): COVID-19 Observational Study (3U01HL123009)
Effort: 0.6 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Gayle Jones, jonesgt@mail.nih.gov
Performance Period: 04/24/2020 – 04/23/2022
Funding Amount: (subcontract)
Project Goals: This study is a national biorepository assembling clinical and biologic specimens with the goal of delineating disease mechanisms and novel therapeutic approaches for COVID-19
Overlap: None

Title: Pulmozyme to Improve COVID-19 ARDS Outcomes (Raby)
Effort: 0.3 calendar months
Supporting Agency: Boston Children's Hospital (subcontract)
Grants Officer: Clinical Trials Business Office (CTBO), CTBO@childrens.harvard.edu
Performance Period: 05/01/20 – 10/30/21
Funding Amount: direct costs
Role: Site PI
Project Goals: The aim of this project is to conduct a randomized, double-blind, placebo-controlled Phase II trial to evaluate the efficacy of inhaled Dornase alfa (pulmozyme) in mechanically ventilated patients with COVID-19 pneumonia.
Overlap: None

ACTIVE GRANTS

Title: PET/CT-Guided Personalized Mechanical Ventilation to Minimize Ventilator-Induced Lung Injury (5R01HL121228)
Effort: 1.0 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:
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: 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 – 09/14/2023 (NCE)
Funding Amount: direct costs
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:
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 – 08/31/2023 (NCE)
Funding Amount:
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

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (1R633HL153011)
Effort: 2.4 Calendar Months (PI)
Supporting Agency: NIH/NHLBI
Grants Officer: Zhou, Guofei (guofei.zhou@nih.gov)
Performance Period: 09/01/2022 – 08/31/2025

Funding Amount: direct costs
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 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: Monitoring pro-resolving leukocyte responses in peripheral blood predicts clinical severity during sepsis (1R21GM144829-01)
Effort: 0.6 Calendar Months in Years 1-2 (R21 Phase), 2.4 Calendar Months in Years 3-4 (R33 Phase) (Co-Investigator)
Supporting Agency: NIH/NIGMS
Grants Officer: Anna Hahn, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES, hahnann@mail.nih.gov (301) 594-5506
Performance Period: 01/01/2022 – 12/31/2023
Funding Amount:
Project Goals: The goals of this grant are to develop an improved understanding of the resolution defects that unleash unrestrained inflammation of sepsis with a longer term goal for new therapeutic targets and prognostic indicators of disease progression.
Specific Aims: Aim 1. Demonstrate reproducible isolation and functional analysis of PMNs from capillary blood. Aim 2. Demonstrate ability to obtain deep proteomic and phosphoproteomic profiles from small numbers of PMNs. Aim 3. Longitudinal analysis of SPM pathway activation during sepsis resolution. Aim 4. Inference and model generation and testing with ex vivo assays.
Overlap: None

Title: 1/2 Ganciclovir To Prevent Reactivation Of Cytomegalovirus In Patients With Acute Respiratory Failure And Sepsis (6UH3HL147011-03)
Effort: 0.12 Calendar Months in Years 1-5 (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Ronald Caulder Grants Management Officer NATIONAL HEART, LUNG, AND BLOOD INSTITUTE caulderr@nhlbi.nih.gov 301.827-8020
Performance Period: 04/01/2022 – 08/31/2027
Funding Amount:
Project Goals: 1. In year 1, we will perform all duties for study start up and implementation including site coordination, IRB and regulatory approvals, hospital training for nurses and physicians, and providing input into creation of databases and forms. 2. We will attend a start up and training meeting during the first year of the award period in Seattle for all study investigators and personnel to be trained in study procedures. We may again attend training meetings via calls or a webinar as needed. During any subsequent meetings, study progress will be discussed and all study personnel will receive refresher training in study procedures, interventions, and outcomes assessments.
Overlap: None

Title: Pulmonary Drug Development
Effort: 2 calendar months
Supporting Agency: Bayer, AG

Grants Officer: Seema Basu, ssbasu@PARTNERS.ORG
Performance Period: 09/20/2019 – 09/19/2024
Funding Amount: per year
Project Goals: Joint laboratory for the research of new treatments for chronic lung diseases with a focus on COPD.
Overlap: none

PENDING GRANTS

Title: Improving Lung Protective Ventilation (ProLung) via Real-time Automated Detection and EHR Decision Support
Effort: 0.6 Calendar Months in Years 1-4 (Co-Investigator)
Supporting Agency: NIH
Grants Officer: TBD, grant unassigned
Performance Period: 04/01/2023 – 03/31/2027
Funding Amount:
Project Goals: To determine rates of compliance with low tidal volume ventilation in ARDS patients and devise a tool to alert clinicians to non-compliance and improved mechanical ventilation parameters.
Overlap: None

Title: Deep phenotyping and pathogen driven heterogeneity of the host immune response in ARDS, Pneumonia, and Sepsis
Effort: 0.3 Calendar Months in Years 1-2, 0.6 Calendar Months in Years 3-6 (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: TBD, grant unassigned
Performance Period: 04/01/2023 – 03/31/2029
Funding Amount:
Project Goals: The Brigham and Women's Hospital (BWH) will participate as part of a Clinical Center as part of the multi-site ARDS, Pneumonia, and Sepsis Phenotyping Consortium (APS Consortium) to understand the heterogeneity and underlying mechanisms of critical illness syndromes and recovery, as well as the relationship and biological overlap among these syndromes.
Overlap: None
Title: Variable Ventilation to Reduce Ventilator-Induced Lung Injury in ARDS
Effort: 0.96 Calendar Months in Year 1, 1.2 Calendar Months in Years 2-4 (Co-Investigator)
Supporting Agency: DOD
Grants Officer: TBD, grant unassigned
Performance Period: 04/01/2023 – 03/31/2027
Funding Amount:
Project Goals: Brigham and Women’s Hospital will screen ICU study subjects with the goal of recruiting and enrolling 15 ARDS subjects over the proposed study period for this proposal testing Variable Ventilation as a mode of mechanical ventilatory support.
Overlap: None

OTHER SUPPORT

Mark A. Perrella, M.D.

PREVIOUS (active within past 5 years)

1. Title: "The Functional Consequences of the 17q12 Asthma Susceptibility Locus"
   Major 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.
   Project Number: 5R01 HL117837
   Name of PD/PI: Raby, B.
   Source of Support: NIH/NHLBI
   Source of Support Address: NIH/NHLBI Information center, P.O Box 30105, Bethesda, MD 20824-0105
   Contracting/Grants Officer: Weiniu Gan; ganw2@nhlbi.nih.gov
   Project/Proposal Start and End Date: 07/01/2015 – 06/30/2019
   Total Award Amount (including Indirect Costs): per year
   Person Months: 0.36 CM
   Overlap: none

2. Title: Phase 2 Study of Safety, Tolerability, and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease
   Major Goals: 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.
   Project Number: Investigator Initiated Clinical Trial
   Name of PD/PI: Rosas, I.O.
   Source of Support: Genentech / Roche
   Project/Proposal Start and End Date: 04/01/2016 – 03/31/2021
   Total Award Amount (including Indirect Costs):
   Person Months: 1.2 CM
   Overlap: none

3. Title: Regulation of Neutrophil Function by Mesenchymal Stromal Cells During Sepsis

Major 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.

Project Number: GM118456

Name of PD/PI: Perrella, M.A.

Source of Support: NIH/NIGMS

Source of Support Address: 45 Center Drive, MSC 6200, Bethesda, Maryland 20892-6200

Contracting/Grants Officer: Anna Hahn; hahnann@mail.nih.gov

Project/Proposal Start and End Date: 05/10/2016 – 02/28/2021

Total Award Amount (including Indirect Costs):

Person Months: 2.74 CM

Overlap: none

4. Title: Systems Biology of Airway Disease

   Major Goals: The overarching goal of the program project, "Systems Biology of Airway Disease", is to identify common molecular determinants and pathways for asthma and COPD.

   Specific Aims: 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.
   Project Number: 5 P01 HL132825

   Name of PD/PI: Weiss, S.

   Source of Support: NIH/NHLBI

   Source of Support Address: NIH/NHLBI Information center, P.O Box 30105, Bethesda, MD 20824-0105

   Contracting/Grants Officer: Suzanne White; whitesa@nhlbi.nih.gov

   Project/Proposal Start and End Date: 09/01/2016 – 07/31/2022

   Total Award Amount (including Indirect Costs): Functional Genomic Core per year

   Person Months: 0.6 CM

   Overlap: none

CURRENT

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

Major Goals: we propose developing MSCs and toll-like receptor 9 agonist (CpG-ODN) pre-conditioned MSCs as cellular therapeutics to reduce the mortality and morbidity of radiation exposure injuries.

Specific Aims: 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.

Project Number: 5U01AI138318

Name of PD/PI: Lederer, J.A.; Perrella, M.A.

Source of Support: NIH/NIAID

Source of Support Address: *5601 Fishers Lane MSC 9806. Bethesda, MD 20892-9806*

Contracting/Grants Officer: Carmen Rios, PhD; Carmen.Rios@nih.gov

Project/Proposal Start and End Date: 04/01/2018 – 03/31/2023

Total Award Amount (including Indirect Costs):

Person Months: 2.4 CM

Overlap: none

2. Title: A Phase 2 Study of Inhaled CO for the Treatment of ARDS
   Major 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).
   Project Number: W81XWH1810667
   Name of PD/PI: Weingarten, J.
   Source of Support: DoD
   Source of Support Address: Grants.gov
   Contracting/Grants Officer: Sandy Snyder; sandy.j.snyder.ctr@mail.mil
   Project/Proposal Start and End Date: 09/15/2018 – 09/14/2023
   Total Award Amount (including Indirect Costs):
   Person Months: 1.2 CM
   Overlap: none

3. Title: Mesenchymal Stromal Cells, Autophagy, and the Host Response to Systemic Bacterial Infection
   Major Goals: To determine whether autophagy is a key mediator in regulating the ability of CO (*ex vivo*) to enhance MSC function in experimental models of sepsis, both by cell-to-cell and paracrine actions of MSCs.

Specific Aims: 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.

Project Number: GM136804

Name of PD/PI: Perrella, M.A.

Source of Support: NIH/NIGMS

Source of Support Address: 45 Center Drive, MSC 6200, Bethesda, Maryland 20892-6200

Contracting/Grants Officer: Anna Hahn, hahnann@mail.nih.gov

Project/Proposal Start and End Date: 04/01/2020 – 01/31/2024

Total Award Amount (including Indirect Costs):

Person Months: 3 CM

Overlap: none

4. Title: Pulmonary Drug Development

   Major Goals: Joint laboratory for the research of new treatments for chronic lung diseases with a focus on COPD.

   Project Number: No award number

   Name of PD/PI: Levy, B.D.

   Source of Support: Bayer, AG

   Project/Proposal Start and End Date: 09/20/2019 – 09/19/2024

   Total Award Amount (including Indirect Costs):

   Person Months: 2.4 CM

   Overlap: none

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

   Major 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.

   Project Number: R61/R33 HL153011

   Name of PD/PI: Choi, A.M.K.; Baron, R.M.

   Source of Support: NIH/NHLBI

   Source of Support Address: NIH/NHLBI Information center, P.O Box 30105, Bethesda, MD 20824-0105

   Contracting/Grants Officer: Zhou, Guofei (guofei.zhou@nih.gov)

   Project/Proposal Start and End Date: 09/01/2022 – 08/31/2025

   Total Award Amount (including Indirect Costs): per year

Person Months: 1.2 CM

Overlap: The 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).

PENDING

1. Title: Combining Cell- and RNA-based therapies to target a genetic disease with myopathy and cardiomyopathy
   Major Goals: The overall goal of the project is to determine whether a combined therapeutic approach of antisense oligonucleotide-mediated DNM2 reduction with cell-based therapy is necessary to rescue striated muscle abnormalities (cardiac and skeletal muscle) in Speg-cKO mice.
   Specific Aims: The specific aims of this project are 1) Determine whether delivery of placental-derived trophoblast stem cells (TSCs) into the fetal hearts of *Speg*$^{-/-}$ mice *in utero*, or after birth in *Speg*-cKO mice, results in improved cardiac function and long-term survival; 2) Assess the efficacy of antisense oligonucleotide (ASO)-mediated DNM2 reduction in *Speg*-cKO mice to rescue skeletal muscle function; and 3) Elucidate whether a combined therapeutic approach using TSCs and *Dnm2* ASO will rescue striated muscle abnormalities (cardiac and skeletal) in SPEG-deficient mice.
   Project Number: 1R01AR081386-01A1
   Name of PD/PI: Agrawal, P.; Perrella, M.A.
   Source of Support: NIH/NIAMS
   Source of Support Address: 1 AMS Circle, Bethesda, MD 20892
   Contracting/Grants Officer: Kreider, Stephanie; skreider@mail.nih.gov
   Project/Proposal Start and End Date: 04/01/2023 – 03/31/2028
   Total Award Amount (including Indirect Costs): (BWH subcontract)
   Person Months: 2.4 CM
   Overlap: none

2. Title: The Role of Mesenchymal Stromal Cells in Neutrophil Trained Immunity
   Major Goals: We have shown that mesenchymal stromal cells (MSC), an integral part of the hematopoietic niche, can augment emergency granulopoiesis – an effect that is enhanced when MSCs are preconditioned with CpG (CpG-MSC). CpG DNA is a toll-like receptor 9 (TLR9) agonist has trained immunity inducing activity. The overarching hypothesis is that soluble proteins or extracellular vesicles produced by CpG-MSCs leave histone modifications at enhancers and promoters of myeloid differentiation in c-kit+ HSCs, leaving them poised to not only augment granulopoiesis, but also produce mature neutrophils with enhanced antimicrobial functions.
   Specific Aims: 1) Delineate the in vivo antimicrobial actions of PMNs arising from c-kit+ HSCs reprogrammed by paracrine factors from CpG-MSCs. 2) Identify the cellular changes that occur in PMN progenitor cells in response to paracrine factors from CpG-MSCs. 3) Identify the protein(s) within the CpG-MSC secretome mediating augmented granulopoiesis.
   Project Number: 1 R01 AI175109-01

Name of PD/PI: Lederer, J.A.

Source of Support: NIH/NIAID

Source of Support Address: *5601 Fishers Lane MSC 9806. Bethesda, MD 20892-9806*

Contracting/Grants Officer: Marinik, Madea J. (madea.marinik@nih.gov)

Project/Proposal Start and End Date: 04/01/2023 – 03/31/2028

Total Award Amount (including Indirect Costs):

Person Months: 1.2 CM

Overlap: none

3. Title: Defining Radiation Induced Immune Dysfunction and Recovery Using Systems Immunology

   Major Goals: Exposure to radiation from a nuclear explosion or medical use will cause a range of injuries to the immune system depending on the level of radiation exposure. Immediate complications of radiation injuries will be functional immune deficiencies due to loss of radiation-damaged immune cells as well as a breakdown in natural protective barriers. Although some progress has been made in defining the immunological consequences of radiation injury, there remains large gaps in understanding specific effects of radiation on the immune system that contribute to short and long-term immune dysfunction and deficiencies. The overall hypothesis is that systems immunology approaches will provide the missing data on specific immune system injuries that contribute to the development of radiation-induced immune dysfunction. An additional hypothesis is that by including a beneficial immunotherapeutic into our experimental design, beneficial immunological changes that promote better immune system recovery after radiation injury will be discovered. This beneficial therapeutic is day 3 post radiation treatment with CpG-DNA, a nucleic acid that activates cells that express its specific receptor, called Toll-like receptor 9 (TLR9).

   Specific Aims: 1) To systematically identify acute and recovery profiles of hematopoietic and peripheral immune cell responses to radiation injury and beneficial immunotherapy. 2) To investigate immune consequences of radiation injury on functional innate and adaptive immune responses to infection and vaccination with beneficial immunotherapy.

   Project Number: 1 R01 AI175373-01

   Name of PD/PI: Lederer, J.A.

   Source of Support: NIH/NIAID

   Source of Support Address: *5601 Fishers Lane MSC 9806. Bethesda, MD 20892-9806*

   Contracting/Grants Officer: Lacy, Megan Jin-A; megan.lacy@nih.gov

   Project/Proposal Start and End Date: 04/01/2023 – 03/31/2028

   Total Award Amount (including Indirect Costs):

   Person Months: 1.2 CM

   Overlap: none

SERHAN, CHARLES

PREVIOUS:

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: 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: 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: 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.

Title: Resolution Mechanisms in Acute Inflammation: Resolution Pharmacology (P01GM095467-10)
Effort: 0.96 calendar months
Supporting Agency: NIH/NIGMS
Grants Officer: Martha Garcia (Martha.garcia@nih.gov)
Performance Period: 04/01/16 - 03/31/22
Funding Amount: (Project 1) and (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: 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: direct costs per year for subcontract
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.

Title: Blood Cell Lipoxygenase Products -- Formation and Action (R01GM038765-34)
Effort: 2.6 calendar months
Supporting Agency: NIH/NIGMS
Grants Officer: Martha Garcia (Martha.garcia@nih.gov)
Performance Period: 08/01/18 - 07/31/22
Funding Amount: 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.

CURRENT:

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)
Effort: 1.2 calendar months
Supporting Agency: Army Medical Research and Material Command
Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)
Performance Period: 09/15/2018 – 09/14/2023
Funding Amount: direct costs annually for subcontract
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: Mechanisms of Pro-Resolving Mediators in Periodontal Regeneration (R01DE025020-07)
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: direct costs per year for subcontract
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: Evaluating Resolution Mechanisms for Infectious Inflammation (R35 GM139430-02)
Effort: 8.4 Calendar Months
Supporting Agency: NIH/NIGMS
Grants Officer: Sarah Dunsmore (dunsmores@nigms.nih.gov)
Performance Period: 04/01/2021 – 03/31/2026
Funding Amount: annual direct costs
Project Goals: In this R35 MIRA, the PI is focusing on addressing critical gaps and challenges in the field of resolution of inflammation relevant to human infectious inflammation, sepsis and recurrence. The main overarching question and challenge to be addressed focuses on the general mission of determining whether failed resolution mechanisms in inflammation contribute to poor outcomes in sepsis or its recurrence and to identify these new components.
Specific Aims: 1) What's the impact of recurring infection on resolution mechanisms in inflammation: Are SPM Mechanisms Primed? 2) Phagocyte SPM receptors for RvD4 and cys-SPM that activate resolution-repair? 3) Is human sepsis failed resolution of inflammation involving SPM pathways - receptors?
Overlap: There is no overlap.

Title: Targeting the Active Resolution of Inflammation for Cardiovascular Disease Prevention (1R01HL160799-01)
Effort: 0.6 Calendar Months
Supporting Agency: NIH/NHLBI
Grants Officer: Yuling Hong (yuling.hong@nih.gov)
Performance Period: 12/01/2021 – 11/30/2025
Funding Amount: annual direct costs for subcontract
Project Goals: We will examine functional actions of the relevant CVD-associated specialized proresolving mediators using ex vivo leukocyte assays for inflammatory gene expression and macrophage pro-resolving function. Results from this proposal will identify and validate resolution mediators and pathways that may play a pivotal role in cardioprotection and could have important public health significance since residual inflammatory risk is common and remains undertreated with current therapeutics.
Specific Aims: Aim 1. Evaluate associations of SPMs with future CVD events in apparently healthy women (WHS, 1500 cases), replicating in individuals with chronic inflammation (JUPITER, 418 cases), and atherosclerotic patients enriched with diabetes (CIRT, 421 cases).
Aim 2.a. Examine the associations of circulating levels of SPMs with clinical CVD risk factors (e.g. age, sex, diabetes, obesity, smoking, diet quality, standard lipids) and with downstream biomarkers/cytokines of systemic inflammation (e.g. CRP, IL-6), using WHS for discovery and CIRT/JUPITER for replication.
2.b. Examine genetic determinants of circulating SPMs, using the identity of the genes implicated by SNP associations to better understand biological pathways for mechanistic insights into SPM functions.
Aim 3.a. Assess temporal changes in SPMs from baseline up to 24 months among CIRT patients in relation to concomitant changes in levels of proinflammatory biomarkers and cytokines (e.g. CRP, IL-6, IL-1b), replicating in JUPITER. 3b. Examine modulation of SPMs over time with randomized low-dose methotrexate vs placebo (CIRT) to identify individuals who may derive benefit from methotrexate.
Overlap: There is no overlap.

Title: Conjunctival Goblet Cell Mucin Secretion in Inflammation and Its Resolution (5 R01 EY19470-13)
Effort: 0.06 Calendar Months
Supporting Agency: NIH/NEI
Grants Officer: George Ann McKie (mckiegeo@mail.nih.gov)
Performance Period: 05/01/2022 – 12/31/2023
Funding Amount: annual direct costs for subcontract
Project Goals: Dr. Serhan's laboratory will be responsible in Specific Aim 2 for analyzing the amount of DHA released and RvD1 biosynthesized using LC-MS-MS lipidomics.
Specific Aims: Specific Aim 1 focuses on health and determine which RvD family members (RvD3-6) increase the intracellular [Ca2+] ([Ca2+]i), elevate cAMP, and stimulate mucin secretion in cultured conjunctival goblet

cells. For this and all three aims we will evaluate if there a sex-dependent difference in response. Specific Aim 2 investigates if in health RvD1 uses an autocrine circuit with a GPR32 (receptor) /DHA (precursor)/RvD1 axis to control its biosynthesis. Specific Aim 3 studies disease and in allergic conjunctivitis interrogates which RvD family members (RvD2-6) counter pro-inflammatory mediator stimulated goblet cell increase in [Ca2+]i and secretion, and promote resolution of AED in vivo.
Overlap: There is no overlap.

Title: EPHEDRA: Enhanced PHthisic by Environmental Disruptors of Resolution Agonists (1R01ES033250-01)
Effort: 1.2 Calendar Months
Supporting Agency: NIH/NIEHS
Grants Officer: Srikanth Nadadur (nadadurs@niehs.nih.gov)
Performance Period: 09/01/2022 – 08/31/2023
Funding Amount: annual direct costs
Project Goals: We are determining if select nanoparticles disrupt the natural pro-resolving mediators and resolution mechanisms for inflammation and lead to increased susceptibility for chronic inflammatory disease as well as increased susceptibility to severe viral and bacterial infections.
Specific Aims: 1. Determine the impact of environmental and engineered nanoparticles (NP) on resolution of lung inflammation. 2. Establish the impact of EDR on viral host responses and post-influenza secondary bacterial pneumonia. 3. Determine impact of NP on efferocytosis, lipid mediator eicosanoid-SPM profiles, SPM receptors and SPM rescue.
Overlap: There is no overlap.

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R33HL153011)
Effort: 0.24 Calendar Months (Co-Investigator)
Supporting Agency: NIH/NHLBI
Grants Officer: Zhou, Guofei (guofei.zhou@nih.gov)
Performance Period: 09/01/22 - 08/31/25
Funding Amount: direct costs
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 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).

PENDING: None.

KEY PERSONNEL PREVIOUS/CURRENT/PENDING SUPPORT

JOHNSON-AKEJU, OLUWASEUN

PREVIOUS (last five years)

Project Title: The role of brain glial activation in knee osteoarthritis pain
Time Commitment: 0.36 calendar
Supporting Agency: 5R01NS094306-05 (Loggia), NIH-NINDS National Institute of Neurological Disorders and Stroke
Funding Agency's Contracting/Grants Officer (name/address): Not Available
Performance Period: 04/2016 - 03/2023
Funding Amount:
Brief Description of Project's Goals: In this project, we will use PET/MR imaging to test the hypothesis that low brain levels of the translocator protein (TSPO), which is upregulated in activated glial cells, predict higher likelihood of developing post-TKA pain.
List of Specific Aims: Not Available
Project Role: Co-investigator (committed efforts ended 3/31/2022)
Overlap: None

Project Title: Project 1: Human Studies of Anesthetic Action
Time Commitment: 0.60 calendar
Supporting Agency: 5P01GM118629-05 (Brown, Program Director), NIH-NIGMS
Funding Agency's Contracting/Grants Officer (name/address): Zuzana Justinova, Program Official, zuzana.justinova@nih.gov
Performance Period: 02/2017 - 01/2023
Funding Amount:
Brief Description of Project's Goals: In this program project we will conduct a set of integrated human, primate, rodent, and mathematical modeling studies to decipher the neurophysiological mechanisms of the four most commonly used anesthetic drugs; propofol, sevoflurane, dexmedetomidine, and ketamine.
List of Specific Aims: SPECIFIC AIM 1. Propofol and sevoflurane produce alpha and slowdelta oscillations. In addition, sevoflurane produces theta oscillations at concentrations greater than 1 MAC. SPECIFIC AIM 2. Dexmedetomidine produces spindle and slow-delta oscillations.
SPECIFIC AIM 3. Ketamine produces gamma, theta and slow-delta oscillations.
Project Role: Co-Investigator (committed efforts ended 12/31/2019)
Overlap: None

Project Title: Scheduled Prophylactic 6-hourly IV Acetaminophen to Prevent Postoperative Delirium in Older Cardiac Surgical Patients. A Pragmatic Trial
Time Commitment: 0.12 calendar
Supporting Agency: 5R01AG065554-03 (Subramaniam), Beth Israel Deaconess Medical Center / NIH
Funding Agency's Contracting/Grants Officer (name/address): Marlena Konieczynska, Sr. Research Contract Associate, Beth Israel Deaconess Medical Center, Boston, MA
Performance Period: 09/2019 – 11/2024
Funding Amount:
Brief Description of Project's Goals: The goals of this project are to expand our knowledge of the pathophysiology of delirium, evaluate intravenous acetaminophen as a new preemptive therapeutic strategy for delirium, and enable continued investigation into the pathophysiology delirium and Alzheimer's Disease and Related Dementias.

List of Specific Aims: Not Available
Project Role: Subaward PI (commitment ended 09/30/2022, transferred subaward to Dr. Bardia as subaward PI at MGH)
Overlap: None

CURRENT

Project Title: Pathophysiology of postoperative delirium and the use of biomimetic sleep as a treatment strategy in the CSICU
Time Commitment: 0 calendar
Supporting Agency: 5R01AG053582-05, NIH-NIA National Institute on Aging
Funding Agency's Contracting/Grants Officer (name/address): Kathleen Moy, Grants Management Specialist, moyk@mail.nih.gov,
Performance Period: 09/2016 - 05/2023
Funding Amount:
Brief Description of Project's Goals: The goals of this project are to expand our knowledge of the pathophysiology of delirium, evaluate intravenous dexmedetomidine loading dose as a new preemptive therapeutic strategy for delirium, suggest neurophysiologically based monitoring strategies to preemptively identify patients at high risk for developing delirium, and enable continued investigation into the pathophysiology delirium and Alzheimer's Disease and Related Dementias.
List of Specific Aims: AIM 1: Investigate the benefits of preemptive biomimetic sleep for reducing the risk of delirium in a Randomized Controlled Trial. AIM 2: Investigate mechanisms of delirium using combined PET/MR imaging and serum metabolic profiling. AIM 3: Investigate predictors of delirium from perioperative EEG recordings.
Project Role: PI
Overlap: None

Project Title: Administrative Supplement: Pathophysiology of postoperative delirium and the use of biomimetic sleep as a treatment strategy in the CSICU
Time Commitment: 0.12 calendar
Supporting Agency: 3R01AG053582-05S1, NIH-NIA National Institute on Aging
Funding Agency's Contracting/Grants Officer (name/address): Kathleen Moy, Grants Management Specialist, moyk@mail.nih.gov
Performance Period: 08/2020 - 05/2023
Funding Amount:
Brief Description of Project's Goals: Patients who develop severe COVID symptoms are most commonly older with significant comorbidities and, thus, are especially susceptible to this morbid brain dysfunction. We propose this Maximizing Treatment of Neurological Dysfunction using Intravenous Guanfacine (MENDING) study Administrative Supplement to the NIAsponsored Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) study (R01AG053582, PI: Johnson-Akeju) to investigate the benefits of intravenous (IV) guanfacine. The MENDING study will complement the MINDDS study hypothesis that alpha-2 agonists improve delirium and ADRD outcomes and explore underlying mechanisms of these outcomes. To complete this phase II proof-of-concept trial of IV guanfacine vs. placebo for the treatment of critical illness delirium in patients with and without COVID-19, we will leverage the personnel, mechanistic work, and cognitive assessments from the MINDDS study along with enrollment resources from 3 NIH-funded observational trials – the INSIGHT-ICU study (R01GM120484), the MOSAIC study (K76AG054864), and the BRAIN-ICU-2 study (R01AG058639).

List of Specific Aims: Aim 1: To determine whether IV guanfacine will increase the number of days alive without delirium and coma (DCFDs) over 14 days relative to placebo. Aim 2: To evaluate whether IV guanfacine twice a day will increase days alive and free of mechanical ventilation (VFDs) and days alive and free of the ICU (IFDs) over 28 days relative to placebo. Aim 3: To assess whether IV guanfacine can reduce the development of ADRD after critical illness.
Project Role: PI
Overlap: None

Project Title: Investigation of Sleep in the Intensive Care Unit (ICU-SLEEP)
Time Commitment: 0.12 calendar
Supporting Agency: 5R01NS102190-05 (Westover), NIH
Funding Agency's Contracting/Grants Officer (name/address): Not Available
Performance Period: 04/2018 - 03/2023
Funding Amount:
Brief Description of Project's Goals: The goals of this project are to evaluate various doses of intravenous dexmedetomidine as a preemptive therapeutic strategy for delirium, and enable continued investigation into the sleep hypothesis of delirium and Alzheimer's Disease and Related Dementias.
List of Specific Aims: Not Available
Project Role: Co-Investigator
Overlap: None

Project Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Time Commitment: 0.6 calendar
Supporting Agency: W81XWH1810667 (Weingarten/Choi), Joan & Sanford I. Weill Medical College of Cornell University/DOD
Funding Agency's Contracting/Grants Officer (name/address): Aleta R. Gunsul, MPA, Director, Office of Sponsored Research Administration, 1300 York Avenue, Box 89, New York, NY 10065-4805, subawards-wcmc@med.cornell.edu
Performance Period: 09/2018 - 09/2023 (NCE)
Funding Amount:
Brief Description of Project's Goals: The major goal of this project is to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure. List of Specific Aims: Not Available
Project Role: Subaward PI Overlap: None

Project Title: 1/2: An Anesthesia-Centered Bundle to Reduce Postoperative Pulmonary Complications: The PRIME-AIR Study
Time Commitment: 0.12 calendar
Supporting Agency: 7UH3HL140177-04 (Vidal Melo), Trustees of Columbia University in the City of New York (The) / NIH
Funding Agency's Contracting/Grants Officer (name/address): William J. Berger, Assistant Vice President, subawards-cumc@columbia.edu
Performance Period: 03/2022 - 02/2024
Funding Amount: based on per patient enrolled
Brief Description of Project's Goals: This is a CSA under Dr. Vidal Melo's UH3 award from Columbia University to MGH: 1. Screen and enroll patients for the proposed protocol, 2. Implement the study as defined by the specific provided instructions, 3. Provide adequate documentation required for the project including timely entry of electronic case report forms made available by the Data Coordinating Center, and 4.

Support the implementation of the central IRB at the local level including facilitation of the communication with the corresponding local IRB.
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: Subaward PI
Overlap: None

Project Title: Investigation of a Novel Biomarker of Postoperative Delirium
Time Commitment: 0.36 calendar
Supporting Agency: 1R21AG073750-01A1 (Johnson-Akeju/McKay), NIH-NIA
Funding Agency's Contracting/Grants Officer (name/address): Susan Zieman, Program Official, ziemans@nia.nih.gov
Performance Period: 06/2022 - 05/2024
Funding Amount:
Brief Description of Project's Goals: The goals of this study are to investigate the temporal expression of metabolic proteins, systemic metabolite levels, and mitochondrial function in older patients during the perioperative period as prognostic measures of postoperative delirium severity scores.
List of Specific Aims: Specific Aim 1. To define the temporal expression of metabolicregulating proteins in serum and investigate their association with delirium in a prospective observational trial. Specific Aim 2. To determine if perioperative changes in systemic metabolite levels and mitochondrial function are correlated with delirium.
Project Role: Contact PI
Overlap: None

Project Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Time Commitment: 1.2 calendar
Supporting Agency: R33HL153011 (A. Choi/ R. Baron), NIH-NHLBI
Funding Agency's Contracting/Grants Officer (name/address): Zhou, Guofei (guofei.zhou@nih.gov)
Performance Period: 09/2022 – 08/2025
Funding Amount:
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: 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.
Project Role: Co-Investigator
Overlap: This 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 Phase Ib will 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).

PENDING

Project Title: Local and Network Representation and Modulation of Human Odor Perception

Time Commitment: 0.6 calendar
Supporting Agency: NIH
Funding Agency's Contracting/Grants Officer (name/address): Not Applicable
Performance Period: 09/2023 - 08/2028
Funding Amount:
Brief Description of Project's Goals: This project will be a comprehensive approach to understanding the cortical-striatal-thalamic-limbic olfactory network. Major goals of the project are to (1) map the spatiotemporal dynamics of odor-specific gamma local field potentials, (2) define odor-specific firing patterns in brain regions associated with olfaction, and (3) manipulate odor perception using electrical stimulation. List of Specific Aims: Not Available
Project Role: Co-Investigator/Richardson (PI),
Overlap: None

Project Title: Pathophysiology of Delirium After Major Cardiac Surgery
Time Commitment: 2.4 calendar
Supporting Agency: NIH
Funding Agency's Contracting/Grants Officer (name/address): Not Applicable
Performance Period: 04/2023 - 03/2028
Funding Amount:
Brief Description of Project's Goals: The major goal of this project is to identify and validate biomarkers associated with the development of postoperative delirium using an integrated systems approach.
List of Specific Aims: Aim 1: Evaluate whether dexmedetomidine regulates the T-tau, P-tau181, and P-tau217 findings associated with major cardiac surgery and postoperative delirium (n = 335). Aim 2: Implement unsupervised clustering of -omics data adjusted for relevant covariates to identify and improve interpretation of postoperative delirium mechanisms using a nested casecontrol study design (n = 38 dexmedetomidine arm [24 control, 14 delirium] and 48 placebo arm [24 control, 24 delirium]). Exploratory Aim 3: Examine associations between polygenic scores and postoperative delirium. Hypothesis. Genetic risk for shorter and excessive sleep duration will be associated with higher postoperative delirium risk.
Project Role: PI
Overlap: None

Project Title: Multiscale Circadian and Genetic Predictors of Delirium and Conversion to Alzheimer's Disease and Related Dementias
Time Commitment: 0.36 calendar
Supporting Agency: NIH
Funding Agency's Contracting/Grants Officer (name/address): Not Applicable
Performance Period: 04/2023 - 03/2028
Funding Amount:
Brief Description of Project's Goals: The major goal of this project is to investigate the impact of sleep/circadian features derived from daily motor activity (actigraphy) recordings on POD risk and progression to AD/ADRD.
List of Specific Aims: Aim 1: Construct and test an integrated sleep/circadian biomarker for POD risk. Aim 2: Examine the genetic basis of POD and whether the integrated biomarker interacts with or mediates genetic risk for POD. Aim 3: Elucidate plasma proteomic mechanisms by which the integrated biomarker affects POD risk.
Project Role: Co-Investigator / Gao (PI) Overlap: None

KEY PERSONNEL CURRENT/ PREVIOUS/ PENDING SUPPORT

THOMPSON, B. TAYLOR

PREVIOUS (last five years)

Title: Precision Medicine in the Acute Respiratory Distress Syndrome
Time Commitments: 5% (0.60 CM)
Supporting Agency: NHLBI- National Heart, Lung and Blood Institute,
Grants Officer: Lora Reineck M.D., M.S | lora.reineck@nih.gov | 5R35HL140026-03
Address: Two Rockledge Center, Suite 10042 6701
Rockledge Dr. MSC 7952
Bethesda, Maryland 20892-7952
Performance Period: 01/16/2018-12/31/2021
Level of funding:
Project 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: Co-Investigator
Overlap: None

Title: Outcomes Related to COVID-19 treated with Hydroxychloroquine among in-patients with symptomatic Disease (ORCHID) **Supporting Agency:** NIH/NHLBI
Grants Officer: Lora Reineck M.D., M.S.| lora.reineck@nih.gov | 3U01HL123009-06S1
Performance Period: 04/15/2020-04/14/2021
Level of funding:
Project Goals: The primary goal is to determine the effectiveness of Hydroxychloroquine.
Specific Aims: The specific aims of this project are to determine the safety and efficacy of hydroxychloroquine versus placebo for hospitalized patients with confirmed COVID-10
Role: PI
Overlap: None

Title: PETAL COVID-19 Observational Study (CORAL)
Supporting Agency: NIH/NHLBI
Grants Officer: Lora Reineck M.D., M.S.| lora.reineck@nih.gov | 3U01HL123009-06S2
Performance Period: 04/24/2020-04/23/2021
Level of funding:
Project Goals: deep phenotyping of COVID-19 patients.
Specific Aims: The specific aims of this project are to conduct retrospective and prospective observational studies (n=3,000) patients with COVID-19, including collection of biospecimens and imaging in a subset of patient admitted to ICUs.
Role: PI
Overlap: None

Title: Use of advanced imaging techniques to improve diagnostic methods for ARDS **Supporting Agency:** NIH/NHLBI
Grants Officer: Lora Reineck M.D., M.S.| lora.reineck@nih.gov | 5R01HL119344-05

Performance Period: 01/01/2014-12/31/2019
Level of funding:
Project Goals: This project will research modern advances in imaging and blood testing methods to improve techniques in diagnosing ARDS.
Specific Aims: 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.
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

CURRENT

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Time Commitments: 10% (1.20 CM)
Supporting Agency: Army Medical Research and Material Command
Contracting/Grants Officer: Snyder, Sandy | sandy.j.snyder.ctr@mail.mil |W81XWH1810667
Performance Period: 09/15/2018-09/14/2023 NCE
Level of funding:
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: Aim1: to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS;
Aim2: 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
Overlap: None

Title: CCC for NHLBI Prevention and Early Treatment of Acute Lung Injury PETAL Network
Time Commitments: 40% **(**4.8 CM)
Supporting Agency: NHLBI- National Heart, Lung and Blood Institute,
Grants Officer: Lora Reineck M.D., M.S | lora.reineck@nih.gov | 5U01HL123009-07
Address: Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952
Bethesda, Maryland 20892-7952
Performance Period: 04/01/2014-10/31/2022 Extension
Level of funding:
Project Goals: This an extension to NHLBI award to the Coordinating Center of the Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. The major goal of this project is 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: PI
Overlap: None

Title: Investigation of Sleep in the Intensive Care Unit (ICU-SLEEP)
Time Commitments: 5% (0.60 CM)
Supporting Agency: NIH-National Institutes of Health
Grants Officer: Janet He, PhD | hey@ninds.nih.gov | 5R01NS102190-04
Address: NINDS - Neuroscience Center, Division of Extramural Activities
6001 Executive Boulevard Suite 3309,
Bethesda, Maryland 20892
Performance Period: 04/01/2018-03/31/2023
Level of funding:
Project Goals: 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 **Specific Aims:** 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

Title: 1/2: An Anesthesia-Centered Bundle to Reduce Postoperative Pulmonary Complications: The PRIME-AIR Study
Time Commitments: 2% (0.20 CM)
Supporting Agency: NHLBI- National Heart, Lung and Blood Institute,
Grants Officer: Lora Reineck M.D., M.S.| lora.reineck@nih.gov | 5UH3HL140177-03
Address: Two Rockledge Center, Suite 10042
6701 Rockledge Dr. MSC 7952
Bethesda, Maryland 20892-7952
Performance Period: 03/19/2019-02/29/2024
Level of funding:
Project Goals: The goal of this randomized controlled trial is to test whether a new anesthetic-centered bundle reduces the rates of PPCs after abdominal surgery, the field with the largest absolute number of those complications.
Specific Aims: 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.
Aim 2: To assess the effect of the proposed bundle on plasma levels of lung injury biomarkers.
Role: Co-Investigator
Overlap: None

Title: International Coordinating Center (ICC) for ACTIV-3 Trial Initiative

Time Commitments: 10% (1.20 CM)
Supporting Agency: NHLBI via Research Triangle Institute
Grants Officer: Antonello Punturieri, M.D., Ph.D.| punturieria@nhlbi.nih.gov |1OT2HL156812
Address: Two Rockledge Center, Suite 10042
6701 Rockledge Dr. MSC 7952
Bethesda, Maryland 20892-7952
Performance Period: 06/01/2020-05/31/2023
Level of funding:
Project Goals: The goal is to conduct clinical trials of monoclonal antibodies for the treatment of COVID19.
Specific Aims: This award supports the design and interpretation of the ACTIV-3 Master Protocol and the coordination of this Master Protocol at PETAL Sites in the United States through the International Coordinating Center at the Massachusetts General Hospital.
Role: Co-Investigator
Overlap: None

Title: Biomarkers of Interstitial Lung Abdormalities Predict Poor Outcomes in ARDS
Time Commitments: 1% (0.12 CM)
Supporting Agency: NIH-NHLBI National Heart, Lung, and Blood Institute
Contracting/Grants Officer: Guofei Zhou, Ph.D.|guofei.zhou@nih.gov | 5R21HL145246-02
Address: Two Rockledge Center, Suite 10042
6701 Rockledge Dr. MSC 7952
Bethesda, Maryland 20892-7952
Performance Period: 09/01/2019- 05/31/2023
Level of funding:
Project Goals: investigating newly discovered pathobiological mechanisms important to onset and progression of ARDS, in identifying factors that account for individual differences in pathobiology and response to treatment and clinical management of ARDS, and in developing and optimizing novel diagnostic (and ultimately therapeutic) strategies to detect, prevent, treat, and cure ARDS**.**
Specific Aims: 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.
Role: Co-Investigator
Overlap: None

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS
Time Commitment: 10% (1.2 CM)
Supporting Agency: NIH-NHLBI National Heart, Lung, and Blood Institute
Contracts/Grants Officer : Zhou, Guofei (guofei.zhou@nih.gov) | R33HL153011
Address: Two Rockledge Center, Suite 10042
6701 Rockledge Dr. MSC 7952
Bethesda, Maryland 20892-7952
Performance Period: 09/2022 – 08/2025
Level of funding:
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.
Role: Co-Investigator

Overlap: This 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 Phase Ib will 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).

PENDING

Title: ARDS, Pneumonia, Sepsis, Phenotyping Consortium (APSP Consortium) Coordinating Center
Time Commitments: 5% (0.6 CM)
Supporting Agency: NIH - NHLBI
Contracting/Grants Officer: Louis Velasco | louis.velasco@nih.gov
Address: Two Rockledge Center, Suite 10042
6701 Rockledge Dr. MSC 7952
Bethesda, Maryland 20892-7952
Performance Period: 4/1/2023 - 3/31/2024
Level of funding:
Project Goals: The proposed Coordinating Center will lead the planning and conduct of a large research study of hospitalized adults with APS, which will generate key information on the causes of APS and what determines recovery. The outcomes of this study will inform the development of new APS treatment strategies.
Specific Aims: Specific Aim 1: Provide leadership in the development and conduct of the APSP Consortium longitudinal study and other Consortium-wide research investigations.
Specific Aim 2: Provide data management and secure data storage, rigorous statistical analyses, and data sharing for APSP Consortium research studies.
Specific Aim 3: Establish a Skills Development Core and disseminate Consortium-generated resources.
Role: Co-Investigator
Overlap: None

SUPPORT

WELTY-WOLF, KAREN

Dr. Welty-Wolf holds a 12-month Duke University appointment and also has non-University appointments and 7/8ths at the Durham Veterans Affairs (VA) Healthcare System. Dr. Welty-Wolf has 5.04 calendar months available for activities at Duke University.

DUKE CURRENT

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Time Commitment: 1.26 calendar months
Supporting Agency: Weill Medical College of Cornell University/ SUB 181691-02
Department of Defense/ W81XWH1810667
Contracting/Grants Officer: Lisa M. Sawyer Phone: Email: lisa.m.sawyer22.civ@mail.mil **Performance Period:** 09/15/2018 – 09/14/2023 (NCE)
Funding Amount:
Brief Description of Project 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, 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: Mitochondrial Quality Control and Alveolar Damage Resolution After Acute Lung Injury
Time Commitment: 0.12 calendar months
Supporting Agency: NIH/NHLBI 5R01-HL135239
Contracting/Grants Officer: Louis Velasco, louis.velasco@nih.gov
Performance Period: 08/10/2017-12/31/2022
Funding Amount:
Brief Description of Project Goals: This project aims to defines the mitochondrial quality control (QC) network in the lung as a therapeutic target during acute lung injury (ALI/acute respiratory distress syndrome; ARDS), a major critical illness caused by injury to the alveolar-capillary barrier. Successful completion of these Aims will provide new information on mitochondrial turnover in AT2 cells during ALI in vivo as well as the first data on the extent to which recovery of alveolar-capillary barrier function depends on an intact inducible mitochondrial QC network in AT2 cells. Proof-of-principle will provide information on the resolution phase of injury and experimental support and rationale for mitochondrial-targeted pharmacological therapy for ALI in patients. **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 necroptosis 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 a) HO-1 or b) NRF-1 in AT2 cells using the approaches of Aim 1.
Overlap: None
Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R33)
Time Commitment: 3.0 calendar months (Site PI)
Supporting Agency: Weill Cornell Medicine/NIH/NHLBI R33 HL153011

Contracting/Grants Officer: Zhou, Guofei (guofei.zhou@nih.gov)
Performance Period: 09/01/2022 – 08/31/2025
Funding Amount: Total Costs
Brief Description of 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-ForsterKane (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 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)

VA CURRENT

Title: Mechanisms of Alveolar Mitochondrial Damage and Resolution in Pneumonia
Time Commitment: 3.0 calendar months
Supporting Agency: Veterans Administration (5 I01 BX004289-02)
Contact Name and Address: Veterans Administration, Box 004289-01A2
Performance Period: 10/01/2019 – 09/30/2023
Level of Funding: Direct Costs
Goals/Aims: The goal of this project is to study the regulation of mitochondrial quality control (MQC), which includes mitochondrial biogenesis and mitophagy, and to determine how this results in cell and lung protection through the prevention of mtDNA oxidation and its extracellular release during life-threatening S. aureus infections. The proposal specifically addresses the lack of information on how MQC, a known critical lung cell defense, contributes to cell survival and ALI resolution, and determines the impact of lung aging on MQC and ALI.
Overlap: None

DUKE PENDING

None

VA PENDING

None

PREVIOUS (last 5 years)

Title: Novel Dialysis-Like Therapeutics in Sepsis-induced Shock and Organ Failure (Welty-Wolf)
Time Commitment: 2.40 calendar months
Supporting Agency: Defense Advanced Research Projects Agency HR0011-15-2-0057
Contracting/Grants Officer: 675 North Randolph St. Arlington, VA. 22203-2114
Performance Period: 9/28/2015 – 05/31/2018
Funding Amount:
Brief Description of Project 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

Other Support

Kraft, Brian

Previous (Last 5 years)

Title: Role of S-nitrosothiols in Akt1 signaling and pneumonia resolution
Time Commitment: 89%/10.68 CM
Supporting Agency: National Institutes of Health – NHLBI (5K08-HL130557-04) Grant Officer: Loius Velasco, louis.velasco@nih.gov
Address: National Heart, Lung and Blood Institute; Building 31
31 Center Drive, Bethesda, MD 20892
Performance Period: 01/15/2017 – 09/19/2021
Level of Funding:
Goals: The central hypotheses of the proposal are that 1) SNOs activate mitochondrial biogenesis in AT2 cells via phosphatase inhibition leading to increased Akt1 phosphorylation and activation of key downstream repair genes; and 2) SNO-mediated induction of mitochondrial biogenesis will accelerate lung repair following bacterial pneumonia.
Aims: 1) Determine regulation of mitochondrial biogenesis in the lung by (a) PTEN and (b) PHLPP, the Akt1-specific phosphatases; and 2) Determine the effects of pharmacologic SNO augmentation on lung repair and cellular metabolism following murine *S. aureus* pneumonia.
Role: Principal Investigator
Overlap: There is no scientific, budgetary or effort overlap

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS
Time Commitment: 5%/0.6 CM
Supporting Agency: Weill Medical College of Cornell University # 200727-02/DOD (W81XWH1810667)
Grant Officer: Aleta Gunsul, Director, Office of Sponsored Research Admin, subawards-wcmc@med.cornell.edu
Address: Weill Medical College of Cornell University
1300 York Avenue, Box 89 New York, NY 10065-4805
Performance Period: 09/15/2018 – 09/14/2020
Level of Funding:
Goals: The 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).
Aims: 1) To evaluate safety, tolerability, and efficacy and to determine the optimal dosing strategy of iCO in patients with ARDS. 2) To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and infammasome activation in patients with ARDS.
Role: Co-Investigator from Duke University
Overlap: There is no scientific, budgetary or effort overlap

Title: ICU Biorepository
Time Commitment: 1%/0.12 CM
Supporting Agency: Duke University, Department of Medicine – Pulmonary Division

Grant Officer: Julia Peterson, Business Administrator for Pulmonary
Address: Julia.peterson@duke.edu
Performance Period: 04/01/2020 – 06/30/2021
Level of Funding: Divisional Funds
Goals: To collect biological samples and clinical data from patients with severe COVID-19 infection in the intensive care unit for future unspecified research.
Role: Principal-Investigator
Overlap: No scientific or budgetary overlap.

Title: IMPALA MOL-PAP-002 A randomized double blind placebo controlled multicentre clinical trial of inhaled molgramostim in autoimmune pulmonary alveolar proteinosis patients
Time Commitment: 2%/0.24 CM
Supporting Agency: Savara Inc.
Grant Officer: Jessica Jackson, Director of Clinical Operations, Jessica.jackson@savarapharma.com;
Address: Savara Inc. 6836 Bee Caves Rd., Bldg III, Ste 200, Austin, TX
Performance Period: 08/20/2018 – 12/19/2019
Level of Funding:
Goals: The primary objective of the study is to compare efficacy of inhaled molgramostim on the Alveolar-arterial oxygen difference ((A-a)DO2) with placebo after 24-weeks treatment.
Aims: 1) To compare efficacy of inhaled molgramostim on Vital Capacity (VC), Diffusion Capacity of the Lung for Carbon Monoxide (DLCO), Forced Expiratory Volume in one (1) second (FEV1), Forced Vital Capacity (FVC) and Arterial oxygen tension (PaO2) with placebo after 24-weeks treatment, 2) To compare efficacy of inhaled molgramostim on the categorical change of (A-a)DO2, VC, DLCO, FEV1, FVC, and PaO2 with placebo after 24-weeks treatment, 3) To compare efficacy of inhaled molgramostim on categorical change in tolerance to exercise with placebo after 24-weeks treatment, 4) To compare efficacy of inhaled molgramostim on dyspnoea, and cough with placebo after 24-weeks treatment, 5) To compare efficacy of inhaled molgramostim on disease severity by Computer Tomography (CT) scoring with placebo after 24-weeks treatment.
Role: Principal-Investigator
Overlap: No scientific or budgetary overlap.

Title: Novel Dialysis-Like Therapeutics in Sepsis-Induced Shock and Organ Failure
Time Commitment: 30%/3.6 CM
Supporting Agency: Defense Advanced Research Projects Agency (HR0011-15-2-0057)
Grant Officer: Susan Shean, susan.shean@darpa.mil
Address: DARPA 675 N. Randolph Street, Arlington, VA 22203-2114
Performance Period: 09/28/2015 - 05/31/2018
Level of Funding:
Goals: The proposed research is designed to test the safety and efficacy of dialysis-based hemadsorption therapy in a non-human primate model of severe sepsis and organ injury. The goal of the study is to demonstrate the effectiveness of Duke's DLT device and of its efforts aimed at developing computational models for predicting the onset of sepsis and optimal treatments for sepsis.
Aims: 1) Perform dose-ranging studies to develop model for *S. pneumonia*e pneumonia with severe sepsis and multiple organ failure, 2) Fully characterize the novel NHP model of

severe sepsis and use as control arm of DLT study, 3) Test the DLT device in uninfected, well animals, 4) Test the DLT device in animals with severe pneumococcal sepsis and multiple organ failure, 5) Perform molecular analyses and cytokine biomarker discovery, 6) Statistical analyses.

Role: Co-Investigator

Overlap: No scientific or budgetary overlap

Current

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS

Time Commitment: 11.667%/1.4 CM

Supporting Agency: Weill Medical College of Cornell University # 200727-02/ DOD (W81XWH1810667)

Grant Officer: Aleta Gunsul, Director, Office of Sponsored Research Admin, subawards-wcmc@med.cornell.edu

Address: Weill Medical College of Cornell University
1300 York Avenue, Box 89 New York, NY 10065-4805

Performance Period: 09/15/2018 – 09/14/2023 (NCE)

Level of Funding: (WU TDC)

Goals: The 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).

Aims: 1) To evaluate safety, tolerability, and efficacy and to determine the optimal dosing strategy of iCO in patients with ARDS. 2) To investigate the effects of inhaled CO on biomarkers of mitochondrial dysfunction and infammasome activation in patients with ARDS.

Role: *09/15/18-09/19/21 Co-Investigator (Duke University)
*09/20/2021 – 09/14/2023 (NCE) Site Principal-Investigator (Washington University)

Overlap: No scientific or budgetary overlap

Title: A Phase 1b Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS

Time Commitment: 2%/0.24 CM

Supporting Agency: Weill Medical College of Cornell University; NIH/NHLBI; R33 HL153011

Grant Officer: Guofei Zhou, guofei.zhou@nih.gov

Performance Period: 09/01/2022 – 08/31/2025

Level of Funding: (WU)

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: Site Investigator/Co-Investigator

Overlap: This 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 Phase Ib will 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: Pilot Study of Safety and Efficacy of Cord Tissue Derived Mesenchymal Stem Cells (hCT-MSC) in COVID-19 Related Acute Respiratory Distress Syndrome (ARDS)
Time Commitment: 1%/0.12 CM
Supporting Agency: The Marcus Foundation
Grant Officer: Ryan Braid, rbraid@marcusfoundation.org
Address: The Marcus Foundation
1266 West Paces Ferry Road, Ste. 615
Atlanta, GA 30327-2306
Performance Period: 05/01/2020 - 11/30/2022
Level of Funding: per patient (anticipated enrollment of 1-2 patients)
Goals: To test the safety and preliminary efficacy of intravenous allogeneic human cord tissue mesenchymal stromal cells (hCT-MSC) as a therapy for acute respiratory distress syndrome (ARDS) due to COVID-19.
Role: Site Principal-Investigator
Overlap: There is no scientific or budgetary overlap.

Pending

Title: The Fluid Responsiveness Evaluation in Patients with Undifferentiated Shock: FRESH-FIRST
Time Commitment: 1.5%/0.18 CM
Supporting Agency: Department of Defense
Grant Officer: NA
Address: NA
Performance Period: 01/01/2023 – 12/31/2026
Level of Funding: (WU)
Goals: The goal of this study is to determine efficacy of precision, dynamic measured guided fluid resuscitation in undifferentiated shock to reduce 90-day mortality and respiratory failure.
Role: Co-Investigator (Reynolds Site PI at WU)
Overlap: No scientific or budgetary overlap

Title: Lung and systemic molecular phenotyping in critical illness
Time Commitment: 1.5%/0.18 CM
Supporting Agency: Vanderbilt University Medical Center; NIH; 1 U01 HL168412-01
Grant Officer: NA
Address: NA
Performance Period: 04/01/2023 – 03/31/2029
Level of Funding: (WU)
Goals: The major goals of this proposal are to (1) establish a three-site clinical center that is part of the NHLBI ARDS, Pneumonia, Sepsis Consortium; (2) complete a 5000 patient longitudinal cohort study of critically ill patients with ARDS, pneumonia and sepsis; and (3) study respiratory phenotypes within this longitudinal cohort study by sampling fluid from the airspaces using heat moisture exchanger filter fluid
Role: Co-Investigator (Singh Site PI at WU)
Overlap: No scientific or budgetary overlap

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:
Not applicable.

QUAD CHARTS:
See enclosed Quad Chart.

9. APPENDICES:
Not applicable

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

PIs: Jeremey A. Weingarten, M.D., 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 2023

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 32 adult patients with ARDS (based on 80% power to detect a difference in change in mtDNA from baseline to day 5 between treatment arms). We will 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