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

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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.					
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1.INTRODUCTION:

Acute respiratory distress syndrome (ARDS) is a devastating disease affecting military, veteran, and civilian populations. ARDS is a syndrome of severe acute lung inflammation and hypoxemic respiratory failure affecting over 180,000 patients annually in the United States with overall mortality rates of 40%. Despite advances in critical care management and lung protective ventilation strategies, ARDS morbidity and mortality remain unacceptably high. The lack of specific effective therapies for ARDS indicates an urgent need for new treatments targeting novel pathways. Low dose inhaled carbon monoxide (iCO) is a novel therapeutic for ARDS supported by compelling data from experimental models of acute lung injury (ALI). We recently completed a Phase I, fixed dose escalation (100 ppm, 200 ppm) trial of iCO in sepsis-induced ARDS, which showed that precise delivery of low dose iCO is feasible and safe in mechanically ventilated ARDS patients. The objective of this study is to further assess safety and evaluate efficacy of low dose iCO therapy in mechanically ventilated patients with ARDS. This multi-center, prospective, randomized, partially double-blind, placebo-controlled Phase II clinical trial will enroll 100 intubated, adult patients with ARDS who will be randomized in a 1:1 ratio to receive either inhaled CO or inhaled air placebo for up to 90 minutes daily for 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 100 adult patients with ARDS (based on 85% power to detect a difference in lung injury score [LIS]) and randomize subjects to iCO or placebo (medical grade air) treatment with a 1:1 randomization scheme.

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

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

Major Tasks and Percent Completion:

Major Task 1: Prepare CO in ARDS Protocol for Implementation- Months 1-4

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.

Major Task 5: Biomarker Assays and Statistical Analysis- Months 6-50

Work has not begun on Major Task 5.

What was accomplished under these goals?

Major Task 1: Prepare CO in ARDS Protocol for Implementation

- 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
Durham VA	3/12/2019	7/29/2019
NYPBMH	2/26/2020	06/24/2020
Duke Regional Hospital	7/2/2020	11/24/2021

- During this reporting period, Protocol v.7.0 was approved by all site local IRBs and by the HRPO on March 15, 2021.

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, two additional sites (NewYork-Prebyterian Brooklyn Methodist Hospital and Duke Regional Hospital) were activated. Site Initiation Visits and training were completed.
- The following trainings were completed for investigators and study staff:
 - o CO ARDS Phase II Study Training Webinar on Protocol v.3.0, study equipment, adverse event reporting, and study database, held on 5/1/2019 for all investigators and study staff.
 - o Coordinator Training Webinar, held on 5/15/2019 and 6/7/2019.
 - o GEM 5000 Training, held on 2/6/2019 and 7/24/2019 for all respiratory therapists and unblinded investigators.
 - o On-site COVent Delivery System training for all respiratory therapists and unblinded investigators, held on 3/19/2019, 3/20/2019, and 3/21/2019.
 - o Training for long-term neurocognitive outcomes assessment was conducted by Dr. Dale Needham's research group at Johns Hopkins University and study coordinators on 2/10/2020 and 2/13/2020. The BWH project manager/study coordinator was certified as a superuser on 3/26/2020 and conducted one-on-one individual training sessions with study coordinators.
 - o All sites completed site initiation visits (SIVs), as well as protocol, study drug delivery, and StudyTrax Database training.

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. The following trainings have been completed by study staff since the last Annual Report:
 - o The site PIs, study coordinators, and additional key personnel continue to have standing bi-weekly teleconference calls to discuss ongoing study conduct and operations, and provide ongoing trainings
 - o A study monitoring visit was conducted at NYPBMH on 5/13/2021. Blinded and unblinded data were reviewed for source verification and database accuracy. Findings were addressed with the site PI and study staff and outstanding items were resolved by the site.
 - o A Site initiation visit was conducted at Duke Regional Hospital on 6/11/2021.
- Remote monitoring of regulatory documents has been ongoing throughout the year.
- The following trainings were completed for new study staff and to refresh current staff in the prior reporting period.
 - o A Coordinator Refresher Training Webinar was held on 6/5/2020.
 - o COVent Delivery System training for respiratory therapists and unblinded investigators at New York-Presbyterian Brooklyn Methodist, held on 8/5/2020.
 - o A study monitoring visit was completed at BWH on 2/13/2020. Blinded and unblinded data were reviewed for source verification and database accuracy. Findings were addressed with the site PI and study staff and outstanding items were resolved by the site.

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

- Major Task 3 has been completed.
- The following documents have been finalized since the last Annual Report:
 - o The Manual of Operations (version 4, dated 4/24/2021) was updated to incorporate recent protocol changes and distributed to all study sites.
 - o The following equipment was purchased for the NYPBMH site:
 - 1 GEM 5000 Co-oximeter from Instrumentation Laboratory (Werfen)
 - 1 Masimo Radical-7 Pulse Oximeter
 - 1 NM3 Monitor
 - 1 Drager Pac 7000 CO Detector
 - NYPBMH will share the 2 COVent Delivery systems from 12th Man Technologies
- The following activities were completed during prior reporting periods:
 - o The DSMB Charter and Statistical Analysis Plan (SAP) were finalized and approved by the DSMB as of 2/17/2019.
 - o The StudyTrax database was finalized and is being used for data entry.
 - o The Manual of Operations (MOP) was finalized as of 5/8/2019 and distributed to all sites.
 - o Five sites have the following equipment on site for the study:
 - 2 COVent Delivery systems from 12th Man Technologies
 - 1 GEM 5000 Co-oximeter from Instrumentation Laboratory (Werfen)
 - 1 Masimo Radical-7 Pulse Oximeter
 - 1 NM3 or NICO Monitor
 - 1 Drager Pac 7000 CO Detector
 - o Equipment Standard Operating Procedures (SOPs) for all the above equipment were created and distributed to all the sites.
 - o Study Drug and Calibration Cylinders from Praxair have been received at all 7 sites. Drug accountability logs have been distributed to all sites and a Master Accountability Log is on file.
 - o A CO ARDS Phase II Lab Manual, Sample Collection Forms, and Sample Labels were created and distributed to all the sites.

Major Task 4: Participant Recruitment, Therapy, Participant Evaluation

- Five sites (BWH, MGH, WCM, Duke University Hospital, Durham VA) were actively screening up until 03/20/2020 when the study was temporarily paused to new enrollment due to the COVID-19 pandemic. With the decline in COVID-19 hospitalizations, screening was re-started in July 2020.
- Due to slower than anticipated enrollment, we have added 2 additional study sites- NY-Presbyterian Brooklyn Methodist Hospital (NYPBMH) and Duke Regional Hospital (DRH). NYPBMH was activated on 11/17/2020. DRH was activated as a new site on 6/11/2021.
- A protocol amendment (version 7) to expand the eligibility criteria was approved by the DSMB and IRB in February 2021. Protocol v.7 was approved by HRPO on March 15, 2021.
- All 7 sites are currently screening their ICUs for potential participants.
- Expanded electronic options to obtain informed consent remotely from subjects' legally authorized representatives (including REDCap, Adobe E-Sign, COVID MyStudies application) during the COVID-10 pandemic were approved by the Mass General Brigham (MGB) IRB.
- Since the last report one additional participant has been enrolled. A total of 4 participants have been enrolled.
 - Two participants were enrolled at BWH on 09/30/2019 (BWH-0012) and 03/04/2020 (BWH-0024), respectively.

- o Subject BWH-0012 completed four out of five days of the study drug treatment and has been followed through 6 months. The subject could not be contacted for the 6-month telephone neurocognitive assessment, despite telephone and mail attempts to contact.
 - o Subject BWH-0024 completed all 5 days of the study drug treatment and was followed up until study day 14. On study day 15 (03/18/2020), the subject suffered a fatal upper gastrointestinal bleed leading to cardiac arrest and death. The Medical Monitor/Data Coordinating Center (DCC) was notified of the serious adverse event (SAE) within 24 hours. The Data and Safety Monitoring Board (DSMB) and Independent Research Monitor were notified within 7 days. A written report was sent from the DCC to the DSMB and Independent Research Monitor within 15 days. The autopsy revealed that the cause of death was due to an acute upper gastrointestinal bleed secondary to gastric and duodenal ulcers. The blinded medical monitor assessment of the event was: serious, unexpected, not related to the study. The unblinded medical monitor agreed with the blinded medical monitor that the inciting event determined at autopsy, acute gastrointestinal hemorrhage, is not related as there is not “a reasonable possibility that the drug caused the event” (21 CFR 312.64(b)). The event was classified as serious, unexpected (not listed in the Investigator’s Brochure), and not related. No change in the study protocol or informed consent form was recommended.
 - o One participant was enrolled at Duke University Hospital (DUH-0024) on 01/22/2020. The subject completed one out of five days of study drug treatment and has been followed through 6 months, including the neurocognitive assessment.
 - o One participant was enrolled at New York-Presbyterian Brooklyn Method (NYP-0009) on 4/4/2021. The subject completed 3 out of 3 days of study drug treatment. On study day 4 (4/9/21), the subject suffered an intracranial hemorrhage ultimately leading to terminal extubation and death on study day 8. The event was classified as serious, unexpected, and probably not related. The Medical Monitors/Data Coordinating Center (DCC) and Data and Safety Monitoring Board (DSMB) were notified of the SAE within 24 hours. The Medical Monitors/DCC agreed with the blinded site investigator that the event was unexpected and probably not related to study drug or study procedures and was likely a complication of severe COVID-19 treated with full-dose anticoagulation. A written report was sent from the Medical Monitors/DCC to the DSMB and Independent Research Monitor within 7 days. The DSMB concurred with the Medical Monitors/DCC assessment that the event was probably not related and recommended that the study should continue without modification. Although the SAE was assessed as probably not related, the event was reported to the FDA within 7 days as it met protocol-specified criteria for an IND safety report because it occurred within the 48-hour time window that defines it as a serious adverse reaction. The site PI notified HRPO of the SAE on 4/20/21.
- A total of 1027 intubated patient records were reviewed across all sites. Two-hundred and eighteen participants met inclusion criteria. Of the participants that met inclusion criteria, 4 participants were enrolled and 214 participants were excluded.

Site	Activation Date	Pre-screened subjects	Met inclusion criteria	Had an exclusion	Enrolled
BWH	6/24/2019	331	47	45	2
WCM	7/1/2019	255	59	59	0

Site	Activation Date	Pre-screened subjects	Met inclusion criteria	Had an exclusion	Enrolled
MGH	8/1/2019	154	41	41	0
Duke University Hospital	9/20/2019	151	47	46	1
Durham VA	9/20/2019	11	3	3	0
NY-Presbyterian Brooklyn Methodist	11/17/2020	86	17	16	1
Duke Regional Hospital	6/11/2021	39	4	4	0
Total		1027	218	214	4

The most common reason for exclusions* were:

- o Severe hypoxemia defined as SpO₂ < 95 or PaO₂ < 80 on FiO₂ ≥ 0.8 (n=39)
- o Stroke (n=44)
 - Protocol versions 1 – 6: Stroke (ischemic or hemorrhagic) or anoxic/hypoxic brain injury or traumatic brain injury (TBI) within the prior 3 months (n=34)
 - 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=10)
- o Moribund patient not expected to survive 24 hours (n=30)
- o Out of window for ARDS onset criteria (n=30)
 - 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=7)
- o Hemoglobin < 7.5 g/dL or hemoglobin < 8 g/dL and actively bleeding (n=22)
- o Use of extracorporeal membrane oxygenation (ECMO) (n=22)
- o Concomitant use of inhaled pulmonary vasodilator therapy (n=21)
- o Acute myocardial infarction or acute coronary syndrome within the last 90 days (n=20)
- o Severe hypoxemia defined as SpO₂ <95 or PaO₂ <90 on FiO₂ ≥ 0.9 (n=18)
- o Patient, surrogate, or physician not committed to full support (n=16)
- o Diffuse alveolar hemorrhage from vasculitis (n=14)

* Please note 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 will add Washington University as an additional enrolling site to help increase enrollment. Bryan Kraft, MD, a Co-Investigator on the trial, is moving to Washington University and will serve as the PI for the new site. Dr. Kraft has been a Co-Investigator and was also a Co-Investigator on the CO ARDS phase I trial (NCT02425579). He is very familiar with the protocol.

- We will obtain HRPO approval at Washington University prior to site activation and initiation of screening.
- We will conduct a site initiation visit and activate Washington University as a new study site.
- We will scrutinize each site's screening practices and continue efforts to enroll patients at all 7 sites.
- We will continue bi-weekly teleconference calls among study personnel to facilitate study goals and discuss issues that may arise.
- We will perform quality control and quality assurance activities, including conducting site monitoring visits.
- We will continue to collect participant study data and specimen collection.
- We will perform biomarker assays.

4.IMPACT:

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

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5.CHANGES/PROBLEMS:

Changes in approach and reasons for change

Not applicable.

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

Over the past year, the COVID-19 pandemic and public health measures to prevent the spread of COVID-19 have had a significant impact on recruitment of participants into our study. In accordance with policies issued from each of our participating institutions due to the COVID-19 pandemic, the study was temporarily paused to new enrollment from 03/20/2020 until August 1, 2020.

To enhance enrollment over the past year, we have added 2 additional sites (New York-Presbyterian Brooklyn Methodist, Duke Regional Hospital) and received approval from our site IRBs to allow enrollment of COVID ARDS patients. To enhance enrollment without compromising participant safety, we have also revised the hypoxemia, anemia, and stroke exclusion criteria. To enhance feasibility of the protocol, we have decreased the duration of study drug treatment from 5 days to 3 days. These protocol revisions (incorporated in protocol v. 7) and permission to enroll COVID-19 subjects have been approved at all study sites.

The ongoing visitor restriction policy at our participating sites due to the COVID-19 pandemic has significant potential to impede enrollment of subjects given the need to obtain consent from the legally authorized representative (LAR) in the majority of patients. We have IRB approval to obtain

consent remotely at several of the sites and have expanded the electronic options of obtaining informed consent remotely including REDCap, Adobe E-Sign, and the COVID MyStudies application. All sites are working to implement electronic options of remote consent based on institutional and local IRB guidelines.

The COVID-19 pandemic still has significant potential to impede enrollment in the study. While we have begun enrolling COVID-19 patients, the declining number of COVID-19 cases and competing trials may impede our ability to enroll COVID-19 patients. In addition, the important public health measures (social distancing, mask wearing, hand washing) taken to combat COVID-19 spread have led to a dramatic decline in the incidence of respiratory viruses such as influenza, which are common etiologies of ARDS, this past year. These public health measures may continue to affect the incidence of ARDS secondary to COVID-19 and respiratory viruses such as influenza and RSV.

To enhance the pace of enrollment, in consultation with our DSMB, we will consider expansion to additional sites, closely monitor screening efforts and enrollment at current sites, and consider additional revisions to the study eligibility criteria including consideration of inclusion of ARDS patients who are on high flow nasal oxygen or non-invasive ventilation. We will review all revisions to the study inclusion and exclusion criteria with the DSMB and submit all protocol amendments to the site IRBs for approval prior to implementation.

Additional delays were encountered in site activation and initiation of screening due to the time required for HRPO approval and due to delay in the delivery of the study product from the manufacturer Praxair. Plans are already underway for addition of Washington University as an additional study site.

Changes that had a significant impact on expenditures

Not applicable.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Not applicable.

Significant changes in use or care of human subjects

Not applicable.

Significant changes in use or care of vertebrate animals

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS:

Publications, conference papers, and presentations

Nothing to report.

- **Journal publications.**

Nothing to report.

- **Books or other non-periodical, one-time publications.**
Nothing to report.
- **Other publications, conference papers and presentations.**
Nothing to report.

Website(s) or other Internet site(s)

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

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

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

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

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

New York-Presbyterian Brooklyn Methodist Hospital

Name: **Jeremy Weingarten**
 Project Role: Principal Investigator (contact) starting 8/1/21
 eRA Commons ID: 78411852
 Nearest person month worked: 0.6 until 7/31/21/ 3 starting 8/1/21
 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 starting 8/1/21
 eRA Commons ID:
 Nearest person month worked: 0.6 starting 8/1/21
 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: **Christina Edwards**
Project Role: Research Coordinator
eRA Commons ID
Nearest person month worked: 1.8
Contribution to Project: Ms. Edwards 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: 1.2 until 7/31/21/ 0.6 starting 8/1/21
Contribution to Project: Dr. Choi is overseeing the research proposal and the overall planning and execution of the clinical trial grant. He contributed to the overall design of the study and oversaw the coordination of sites for the institutional IRB submissions and the advancement of the study according to the timeline.

Name: **Maria Plataki**
Project Role: Site PI/ Co-Investigator
eRA Commons ID: plataki
Nearest person month worked: 6.0
Contribution to Project: Dr. Plataki has overseen the IRB submission and approval at Weill Cornell, has helped coordinate the 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: **Laura Fredenburgh**
Project Role: Site PI/ Co-Investigator
eRA Commons ID: LF1234

Nearest person month worked: 1.38

Contribution to Project: Dr. Fredenburgh has directed the overall design and writing of the Phase II study protocol, coordinated with the sites for IRB submissions, and oversees regulatory reporting to the DCC, DSMB, and FDA. Dr. Fredenburgh directed the trial start-up including developing materials to conduct the study, purchasing trial-related equipment, as well as developing the case report forms and database design. Dr. Fredenburgh is overseeing screening and enrollment of subjects at BWH, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data.

Name: **Rebecca Baron**
Project Role: Co-Investigator/DCC Co-Director
eRA Commons ID: rmb123

Nearest person month worked: 3.0

Contribution to Project: Dr. Baron has assisted with developing materials to conduct the study, participated in the study design, and assisted with development of the case report forms and the statistical analysis plan. Dr. Baron is co-directing the DCC and overseeing regulatory reporting for the trial 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: 8.88
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: **Marcos Vidal Melo**
Project Role: Site PI
eRA Commons ID: MVMELO
Nearest person month worked: 0.51
Contribution to Project: Dr. Vidal Melo supervised the trial management team at MGH including preparations associated with the research coordinator and respiratory therapists. Dr. Vidal Melo is overseeing personnel and equipment for screening and enrollment of subjects, delivery of the study drug to enrolled subjects, study drug monitoring, and retrieval of clinical data.

Name: **B. Taylor Thompson**
Project Role: Co-Investigator/ DCC Co-Director
eRA Commons ID: BTTHOMPSON
Nearest person month worked: 0.3
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: 0.06
Contribution to Project: Dr. Saillant participated in preparing the conduct of the project in the trauma and burn ICUs at MGH.

Name: **Mammary Kone**
Project Role: Clinical Research Coordinator
eRA Commons ID: mamarykone
Nearest person month worked: 0.07 ended 6/30/21
Contribution to Project: Mr. Kone participated in preparing study documentation, equipment, and facilities; IRB submission; and communication with the DCC in preparation for the implementation of the study. Mr. Kone is managing the regulatory aspects of the study and training new staff on Epic review and data collection.

Name: **Hassan Ahmed**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 0.75 ended 6/30/21
Contribution to Project: Mr. Ahmed participated in preparing study documentation, equipment, and facilities. Mr. Ahmed is actively screening subjects for enrollment in the study at MGH.

Name: **Alex Choi**
Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 1.25 starting 7/1/21
Contribution to Project: Mr. Choi participated in necessary training activities and will be responsible for screening subjects for enrollment in the study at MGH.

Name: **Raksha Kothari**
Project Role: Clinical Research Coordinator II
eRA Commons ID:
Nearest person month worked: 1.25 starting 7/1/21
Contribution to Project: Mrs. Kothari participated in necessary training activities and will be 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: **Corey Vatsaas**
Project Role: Co-Investigator
eRA Commons ID: CVATSAAS
Nearest person month worked: 0.24
Contribution to Project: Dr. Vatsaas is preparing for recruitment of subjects in the Duke surgical and trauma ICU populations and assisting with study drug administration in those subjects. Dr. Vatsaas' effort has been assisting with study start-up and screening in the surgical ICUs.

Name: **Bryan Kraft**
Project Role: Co-Investigator
eRA Commons ID: bryankraft
Nearest person month worked: 0.6
Contribution to Project: Dr. Kraft is responsible for conducting and analyzing biomarker studies for mitochondrial Quality Control on isolated blood leukocytes. He is also responsible for assisting with data collection and administration of the study drug for subjects enrolled at Duke Hospital and the Durham VA Hospital.

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: **Allie Frear**
Project Role: Clinical Research Coordinator, Senior
eRA Commons ID:
Nearest person month worked: 0.08
Contribution to Project: Ms. Frear 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: **Brittany McDowell**

Project Role: Clinical Research Coordinator
eRA Commons ID:
Nearest person month worked: 2.8
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: **Haley Neese**
Project Role: Data Manager
eRA Commons ID:
Nearest person month worked: 0.8
Contribution to Project: Ms. Neese is a Data Manager from the Duke Office of Clinical Research. She is responsible for assisting with the development and maintenance of the RedCap eConsent at Duke.

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.

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 Materiel Command

Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)

Performance Period: 02/14/2020 – 09/14/2022

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.

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 Materiel 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) 09/15/2018-09/14/2022 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) 04/01/2018-03/31/2022 0.6 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

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 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)

03/01/2019-02/28/2022

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

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

R61HL153011 (A. Choi/ L. Fredenburgh - Multi-PI) 09/15/2020-08/31/2022 NCE 0.912 calendar months
R33 09/01/2022-08/31/2025

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).

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- β 1 genetic modifiers and Chi3l1 and its receptors in the lung at baseline, after exposure to CS or TGF- β 1 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-13R α 2 glycosylation and epigenetic modifications of IL-13R α 2 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

PENDING SUPPORT

None

COMPLETED SUPPORT

P01 HL108801 (Perrella)

08/15/2011-06/30/2017

1.86 calendar months

NIH/NHLBI (NCE)

Carbon Monoxide: Novel Opportunities for Therapy, Project 1

Role: Project 1 Leader

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

Goals: To improve our understanding on how carbon monoxide mediates its' cytoprotection will assist in the proof of concept studies in humans to examine whether inhaled carbon monoxide can be a potential therapy in human sepsis and acute lung injury.

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

Overlap

None

P01 HL105339 (Silverman)

08/17/2011-06/30/2017

0.6 calendar months

NIH/NHLBI (NCE)

Functional Genetics of COPD

Role: Co-Investigator

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

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

Specific Aims: The three projects in this PPG focus on Genetics (Project 1, PI: Silverman); Gene Expression (Project 2, PI: Choi); and DNA Methylation (Project 3, PI: DeMeo). These projects will build on a substantial existing infrastructure

of well-phenotyped study populations, experience in phenotypic characterization of COPD, and an extensive track record of both in vitro and in vivo functional assessment of COPD pathogenesis. There are likely multiple additional COPD susceptibility loci, which need to be discovered. Some of these genetic loci may be influenced primarily by epigenetic alterations (e.g. DNA methylation) instead of, or in addition to, heritable SNP variation. Moreover, the other gene members of the pathways related to these genetic determinants of COPD are unknown, and assessment of gene expression and DNA methylation can likely provide insight into these pathways. Thus, we have included discovery of additional gene expression and epigenetic influences on COPD susceptibility as a central focus of this PPG. In addition, the actual genetic determinants within the GWAS loci have not been proven. Thus, we have included efforts to localize the key genes within those regions. Multiple approaches will be used to accomplish this goal. Including assessment of genetic association in a population of different genetic ancestry (African Americans from the COPD Gene project), analysis of gene expression among genes within GWAS loci, assessment for epigenetic changes of genes within GWAS loci, and assays of long-range gene regulation (e.g. chromosome conformation capture). In addition to localization of the key determinants, functional validation will be required to confirm that specific genes are involved in COPD pathogenesis and to understand their impact. We will employ both in vitro assessment within lung epithelial and monocyte cell lines (with validation in primary cell types) as well as in vivo assessment in murine models of underexpression (knockout) of the key genes and susceptible vs. resistant Inbred strains which are tested with long-term cigarette smoke exposure.

Overlap

None

R01 HL130826 (B. Ding)

05/01/2016-04/30/2021

0.6 calendar months

NIH/NHLBI

Endothelial cell-derived MMP14 in lung alveolar regeneration and fibrosis

Role: Co-Investigator

Direct Costs:

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

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

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

Overlap

None

Participation ended Jan 2017.

R01 HL129875-01 (N. Dhillon)

09/01/2016-06/30/2020

0.6 calendar months

NIH/NHLBI

Impact of Opiate Abuse on HIV-Mediated Pulmonary Vascular Remodeling

Direct Costs:

Role: Co-Investigator

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

Goals: The hypothesis of our study is that the combined exposure of pulmonary endothelial cells to HIV-protein(s) and morphine results in the induction of autophagy that leads to enhanced proliferation of endothelial cells and severe pulmonary vascular remodeling. We will evaluate the effect of HIV- Tat and morphine on the oxidative stress mediated regulation of bulk autophagy in endothelial cells, delineate the role of autophagy/mitophagy in Tat and morphine mediated enhanced proliferation and focus on in-vivo investigation of PAH and autophagy in HIV-1 Tg rats with or without morphine exposure.

Specific Aims: In the first aim we will evaluate the effect of HIV- Tat and morphine on the oxidative stress mediated regulation of bulk autophagy in endothelial cells. In the second aim, we propose to delineate the role of autophagy/mitophagy in Tat and morphine mediated enhanced proliferation. The third aim will be focused on in-vivo investigation of PAH and autophagy in HIV-1 Tg rats with or without morphine exposure.

Overlap

None

Participation ended Jan 2017.

P01 HL114501 (Choi)

09/06/2013-06/30/2020 Core A: 0.12 CM; Project 1: 0.12 CM

Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers

Direct Costs: (Proj 1), (Core A)

Role: Overall PD/PI; Project 1 Leader; Core A Leader

Name and address of Contracting/Grants Officer: Dr. Antonello Punturieri, Division of Lung Diseases; National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952

Goals: In this program project we have integrated the expertise of investigators from COPD and IPF community, both basic and translational, to come together to better understand the pathogenesis of these chronic lung diseases, and hopefully identify new molecular targets in the treatment of these dreadful diseases in the future.

Specific Aims: We will attempt to reach our goals by the addressing the following projects and cores: **Project 1)**

Homeostatic Role of Autophagy in Lung Emphysema and Fibrosis: Specific Aim 1: Determine whether divergent regulation of autophagy in fibrosis and emphysema is TGF- β 1 dependent or independent **Specific Aim 2:** Determine whether autophagy mediates emphysematous and/or fibrotic responses via mTOR independent or dependent pathway

Specific Aim 3: Determine the role of mitochondria derived reactive oxygen species (ROS) and mitophagy in the development of emphysema or pulmonary fibrosis; **Project 2) Genetic Modifiers of TGF-Beta1 and Cigarette Smoke in Fibrosis and Emphysema- Specific Aim 1:** Define the roles of Wisp-1, Lama1, Sfn, and Plunc in the pathogenesis of TGF- β 1-induced fibrosis. **Specific Aim 2:** Define the roles of Ccna2 and PAI-1 in the pathogenesis of TGF- β 1-induced injury and emphysema. **Specific Aim 3:** Characterize the effects of CS on TGF- β 1-induced fibrosis and emphysema, the expression of the genetic modifiers of these responses and DNA methylation. **Specific Aim 4:** Characterize the expression of TGF- β 1 genetic modifiers in tissues from patients with IPF or COPD. **Project 3) Genetics and Epigenetics of COPD and IPF- Specific Aim 1:** Rare Genetic Determinants of COPD and ILD **Specific Aim 2:** Epigenetic Determinants of COPD and ILD **Specific Aim 3:** System Genetics; **Project 4) Clinical Outcomes and Molecular Phenotypes in Smokers with Parenchymal Lung Disease- Specific Aim 1:** Define the chest CT patterns that predict functional impairment in smokers with ILA and how they impact the clinical progression of patients with COPD **Specific Aim 2:** Demonstrate divergent regulation of TGF- β 1 related molecular pathways in smokers with ILA and IPF patients when compared to patients with COPD **Specific Aim 3:** Identify divergent regulation of novel alveolar macrophage and epithelial cell gene networks in smokers with ILA and patients with IPF and COPD. **Core 1) Administrative Core-** The core will provide administrative support for budgetary and personnel resource management, coordination of regular scientific and review meetings, and regulatory and scientific reporting of the research activities. **Core 2) Respiratory Computational Discovery Core-** The studies proposed in this program project will generate a series of intricate datasets consisting of a variety of data types, including extensive clinical phenotypes, genome-wide genotypes, gene expression and methylation data. **Core 3) Clinical Biorepository Core-** This core aims to recruit, phenotype and sample IPF and COPD patients, smokers with interstitial lung abnormalities and smokers without lung disease. The core will coordinate all human samples (BAL samples, lung tissues, cells) which will be used by all projects of the PPG; **Core 4) Murine Models and Molecular Analysis Core-** The core will provide projects based at BWH with the expertise and resources required for CS induced emphysema and bleomycin and irradiation induced fibrosis in mice. The core will also provide molecular analysis for clinical projects of the PPG.

Overlap

None

R01 HL060234 (M. Choi/ A.M.K Choi - Multi-PI)

03/14/2014-01/31/2020

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 – 09/14/2022

6 calendar months

Department of Defense

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

Role: Co-Investigator

Direct Costs:

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

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

R61HL153011 (A. Choi/ L. Fredenburgh)

09/15/2020 – 08/31/2022

0.36 calendar months

R33

09/01/2022 – 08/31/2025

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: Lora Reineck (lora.reineck@nih.gov)

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

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

Overlap: 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

K08 HL157728 (Plataki)

09/01/2021-08/31/2026

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.

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

PREVIOUS/CURRENT/PENDING SUPPORT:

MARY E. CHOI, MD

ACTIVE GRANTS

P01HL114501 (A. Choi)

06/10/2021-04/30/2026

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

W81XWH1810667 (J. Weingarten/ A. Choi – Multi-PI) 09/15/2018 – 09/14/2022

1.2 calendar months

Department of Defense

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

Role: Co-Investigator

Direct Costs:

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).

R01HL055330 (A. Choi/M. Choi)

04/01/2018 – 03/31/2022

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 A. Reineck, MD, Lung Biology & Disease Program, National Health Lung and Blood Institute; RKL2 BG RM 10171, 6701 Rockledge Dr, Bethesda, MD 20817

Goals: The overall goal is to understand the role of receptor-interacting protein-3 kinase (RIPK3)-dependent necroptosis pathway and inflammation in the pathogenesis of experimental acute lung injury (ALI) and in human disease such as ARDS. The project examines how mechanical injury or infection causes dysregulated fatty acid (FA) metabolism resulting in activation of RIPK3-dependent signaling and necroptosis, and that disruption of FA metabolism promotes macrophage inflammasome activation and pro-inflammatory cytokines production, which contributes to the development of ALI. We also determine whether necroptosis-related proteins and FA are associated with morbidity and mortality in patients with critical illness, including ARDS.

Specific Aims: Aim 1: To determine the regulation and function of RIPK3-dependent necroptosis in ALI. **Aim 2:** To determine the mechanisms by which necroptosis mediates NOX4-dependent NLRP3 inflammasome activation in ALI.

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

Overlap

None

R01DK113088 (L. Gudas)

12/04/2017 – 11/30/2021

0.54 calendar

months

NIH/NIDDK

Gene Nutrient Interactions in Kidney Function

Role: Collaborator

Direct Costs:

Name and address of Contracting/Grants Officer: Krystyna E. Rys-Sikora, PhD, Program Director, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive Kidney Diseases; 9000 Rockville Pike, Bethesda, MD 20892

Goals: We propose to test the hypothesis that renal lipid accumulation is a key contributor to dysfunction in both the glomerular and tubular compartments of the kidney, and that this excess renal lipid accumulation and renal dysfunction can be reversed through the use of an agonist for the retinoic acid receptor $\beta 2$ (RAR $\beta 2$), a member of the nuclear receptor protein family of transcription factors.

Specific Aims: Using both a high fat diet (HFD)-induced model and *db/db* murine model of obesity-associated chronic kidney disease (CKD), we will test our hypothesis by the following specific aims. **Aim 1:** We will test (in preclinical drug efficacy studies) three selective RAR $\beta 2$ agonists (AC261066, AC55649, and CD2314) to determine if these synthetic retinoids can (a) decrease the lipid deposition in the kidneys and (b) improve or stabilize kidney function in obesity-induced CKD. **Aim 2:** We will examine the molecular mechanism(s) by which RAR $\beta 2$ agonists reduce lipid accumulation and renal inflammation using both mouse models. We will also test whether the RAR $\beta 2$ agonists are acting via RAR $\beta 2$ expressed in particular types of cells in the kidney through the use of renal cell type specific RAR β knockout mice. **Aim 3:** To understand the mechanism of action of RAR $\beta 2$ agonists, we will determine whether RAR β agonists act directly on podocytes, mesangial cells, and proximal tubule cells via the RAR $\beta 2$ receptor to modulate metabolism, proliferation, and/or differentiation through the use of cell culture models.

Overlap

None

R01HL133801 (M. Choi/A. Choi)

08/01/2017 – 07/31/2022

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

PENDING GRANTS

R61HL153011 (A. Choi/L. Fredenburgh) 09/01/2022 – 08/31/2025

0.6 calendar months

NIH/NHLBI

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: Lora Reineck, lora.reineck@nih.gov, 301-435-0222

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

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

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

COMPLETED GRANTS

P01HL114501 (A. Choi)

09/06/2013 – 06/30/2020

0.12 calendar

months

NIH/NHLBI

Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers

Role: Co-Investigator (Project 1)

Direct Costs: (Project 1)

Name and address of Contracting/Grants Officer: Dr. Antonello Punturieri, Division of Lung Diseases; National Heart, Lung and Blood Institute; Two Rockledge Center, Suite 10042, 6701 Rockledge Dr. MSC 7952, Bethesda, Maryland 20892-7952

Goals: In this program project we have integrated the expertise of investigators from COPD and IPF community, both basic and translational, to come together to better understand the pathogenesis of these chronic lung diseases, and hopefully identify new molecular targets in the treatment of these dreadful diseases in the future.

Specific Aims: (Project 1) Homeostatic Role of Autophagy in Lung Emphysema and Fibrosis: **Aim 1:** Determine whether divergent regulation of autophagy in fibrosis and emphysema is TGF- β 1 dependent or independent. **Aim 2:** Determine whether autophagy mediates emphysematous and/or fibrotic responses via mTOR independent or dependent

pathway. **Aim 3:** Determine the role of mitochondria derived reactive oxygen species (ROS) and mitophagy in the development of emphysema or pulmonary fibrosis;

Overlap

None

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

R01DK057661 (M. Choi)

06/01/2000 – 05/31/2017

3.6 calendar

months

NIH/NIDDK

TGF-beta Signaling in the Kidney

Role: Principal Investigator

Direct Costs:

Name and address of Contracting/Grants Officer: Dr. Deborah K. Hoshizaki, Division of Kidney, Urologic & Hematologic, National Institute of Diabetes and Digestive and Kidney Diseases, BG 2DEM RM 6143, 6707 Democracy Blvd, Bethesda, MD 20817

Goals: This proposal is focused on examining the mechanism and functional role of TGF- β 1 signaling via TAK1 in renal cells, and the regulation of autophagy and its physiological functional role in an experimental model of renal fibrosis.

Specific Aims: **Aim 1:** To determine the mechanism and functional role of TGF- β 1 signaling via TAK1 in renal cells.

Aim 2: To determine the regulation and function of autophagy induced by TGF- β 1 in renal cells. **Aim 3:** To determine the in vivo physiological functional role of autophagy in an experimental model of renal fibrosis. We will employ state-of-the-art approaches including a variety of dominant negative mutants of the signal transducing molecules, the MAPKs,

focusing on the TAK1-MKK3 signaling axis, gene silencing by the use short interfering RNA (siRNA), and genetically altered mice, the null mice for the various TAK1, MKK3, Caveolin-1, and the autophagy genes, LC3 and Beclin 1.

Overlap

None

5UL1 R000457-09 (O. Akchurin)

06/01/2016 – 05/31/2017

0.12 calendar months

Clinical & Translational Science Center Pilot Award, Weill Cornell Medicine

Growth delay and inflammation in juvenile chronic kidney disease

Role: Co-Investigator

Direct Costs:

Goals: The major goals are to study growth delay and inflammation in high-adenine diet induced CKD in juvenile (growing) mice.

Name and address of Contracting/Grants Officer: Juan J. Cordero, MD, Protocol and Regulatory Manager, Weill Cornell Medicine, Gertrude and Louis Feil Family Research Building (RR Building) 407 East 61st Street, Room: 221 New York, NY 10065-8736

Specific Aims: **Aim 1:** Optimize the high adenine diet regimen in juvenile male and female mice and define its effects on growth rate and inflammation. **Aim 2:** Investigate the role of TNF-alpha antagonist etanercept in uremic growth delay and inflammation using the adenine-induced CKD mouse model.

Overlap

None

PREVIOUS/CURRENT/PENDING SUPPORT:

WINCHELL, ROBERT

PREVIOUS

None

CURRENT

W81XWH1810667 (A. Choi) 09/15/2018 – 09/14/2022 0.24 calendar months

Department of Defense

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

Role: Co-Investigator

Direct Costs:

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

PENDING

None

PREVIOUS/CURRENT/PENDING SUPPORT:

LIZIAMMA GEORGE, MD

ACTIVE

W81XWH1810667 (J. Weingarten/A. Choi) 08/01/2021 – 09/14/2022 0.6 calendar months

Department of Defense

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

Role: Site PI/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

Title: US-based, observational, drug registry of Opsumit® (macitentan) new users in clinical practice

Effort: 0.6 Calendar Months (PI)

Supporting Agency: ACTELION PHARMACEUTICALS LTD

Grants Officer: Kristy L. Bertz

Performance Period: 2/2/2015- open

Funding Amount:

Project Goals: This study is a prospective observational drug registry developed to characterize the safety profile (including primarily potential serious hepatic risks) and to describe clinical characteristics and outcomes of patients newly treated with Opsumit in the post-marketing setting.

Specific Aims: 1. To describe demographic and clinical characteristics of patients newly treated with Opsumit at enrollment and during the observation period. 2. To describe pulmonary arterial hypertension (PAH) treatment patterns at enrollment and during the observation period.

Overlap: There is no overlap.

PENDING

None

PREVIOUS

Title: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of BAY 41-6551 as Adjunctive Therapy in Intubated and Mechanically-Ventilated Patients with Gram-Negative Pneumonia

Effort: 0.6 Calendar Months (PI)

Supporting Agency: Bayer HealthCare Pharmaceuticals Inc.

Grants Officer: Glenn Swann

Performance Period: 7/21/2015- 9/28/2017

Funding Amount:

Project Goals: To evaluate the efficacy (superiority) and safety of BAY 41-6551 as measured by the comparison of the clinical cure rate of aerosolized BAY 41-6551, administered via the PDDS Clinical, versus placebo (normal saline) at the Test-of-Cure (TOC) visit in patients with microbiologically confirmed Gram-negative pneumonia.

Specific Aims: To evaluate the efficacy of BAY 41-6551 (versus placebo) as measured by:

- ☐ The number of days on mechanical ventilation
- ☐ The number of ICU days at Day 28
- ☐ The total number of days of Gram-negative IV antibiotics per patient

- ☐ CPIS changes through TOC
- ☐ The clinical relapse rates at Day 28
- ☐ The all-cause mortality rate during therapy, at Day 15 and at Day 28
- ☐ The number of hospital days at Day 28

Overlap: There is no overlap.

Title: Double-blind, Randomized, Placebo controlled study, Parallel group study to Evaluate the Effect of Aclidinium Bromide on Long-term Cardiovascular Safety and COPD Exacerbations in Moderate to Very Severe COPD Patients

Effort: 0.6 Calendar Months (PI)

Supporting Agency: Forest Research Institute, Inc.

Grants Officer: Wayne Adams

Performance Period: 10/25/2013- 11/26/2016

Funding Amount:

Project Goals: The Objectives of this study are to assess the safety of Aclidinium bromide on major adverse cardiovascular events (MACE), to assess the overall safety of Aclidinium bromide and to assess whether Aclidinium bromide reduces moderate or severe COPD exacerbations. This study is a double-blind, randomized, placebo controlled, parallel-group study to evaluate the effect of Aclidinium bromide on the cardiovascular safety and COPD exacerbations in patients with moderate to very severe COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.

Specific Aims: 1. Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Per Subject Per Year During the First Year of Treatment [Time Frame: 12 months] 2. Number of Participants With Major Adverse Cardiovascular Event (MACE) - on Study Analysis [Time Frame: At Screening, Treatment period (up to 36 months) and Post-treatment follow-up (PTFU)].

Overlap: There is no overlap.

PREVIOUS/CURRENT/PENDING SUPPORT:

FREDENBURGH, LAURA

PREVIOUS:

Title: Carbon Monoxide: Novel Opportunities for Therapy (5P01HL108801-05)

Effort: 2.4 Calendar Months (Core D Co-Director; Project 1 Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Harabin, Andrea L. (andrea.harabin@nih.gov)

Performance Period: 08/15/11 – 06/30/17 (No Cost Extension)

Funding Amount: (Core B) direct costs per year (No Cost Extension)

Project Goals: The major goal of this study is to investigate carbon monoxide as a novel therapy for sepsis and ARDS.

Specific Aims: The specific aims of this project are 1) to elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection; 2) to identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI; and 3) to provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI in Cycle II of the translational PPG program.

Overlap: There is no overlap.

Title: The Inflammasome: A Novel Biomarker in ALI/ARDS (5R01HL112747-04)

Effort: 1.2 Calendar Months (Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)

Performance Period: 05/15/12 – 04/30/17 (No Cost Extension)

Funding Amount: direct costs per year (No Cost Extension)

Project Goals: The major goal of this study is to investigate the role of inflammasome activation in the development of infection-related ALI/ARDS and determine whether statins exacerbate lung injury and inflammation via activation of the inflammasome.

Specific Aims: The specific aims of this project are 1) to determine gene expression and protein levels of the inflammasome during infection-related ALI/ARDS using prospectively collected blood and banked plasma samples from placebo- and statin-treated SAILS subjects; and 2) to determine the cellular localization of expression of the inflammasome complex and role of inflammasome activation on cellular responses and function, using primary neutrophils and monocytes isolated from prospectively enrolled placebo- and statin-treated SAILS subjects, as well as primary cells isolated from control ICU subjects.

Overlap: There is no overlap.

Title: Brigham Research Institute Fund to Sustain Research Excellence

Effort: 0 Calendar Months (PI)

Supporting Agency: Brigham Research Institute Fund, Brigham and Woman's Hospital

Grants Officer: Slavik, Jacqueline M. (jslavik@bwh.harvard.edu)

Performance Period: 07/01/17 – 12/31/17

Funding Amount: direct costs per year

Project Goals: The overall goal of this award is to provide interim support to independent investigators who submitted a non-mentored NIH grant application that was reviewed but missed the funding payline.

Specific Aims: The specific aims are to investigate mechanotransduction and YAP/TAZ signaling in pulmonary arterial hypertension.

Overlap: There is no overlap.

Title: Mechanobiology of Vascular Remodeling in Pulmonary Arterial Hypertension (4R01HL114839-05)

Effort: 3.6 Calendar Months (PI)

Supporting Agency: NIH/NHLBI

Grants Officer: Colombini-Hatch, Sandra (sandra.hatch@nih.gov)

Performance Period: 08/14/12 – 03/31/19 (NCE)

Funding Amount: direct costs per year

Project Goals: The overall goal is to elucidate the role of matrix stiffness on pulmonary vascular remodeling and the pathobiology of pulmonary arterial hypertension.

Specific Aims: The specific aims of this project are 1) to investigate the temporal and spatial increases in PA stiffness and reversibility of mechanical changes during experimental PAH; 2) to determine whether increases in matrix stiffness trigger a “remodeling phenotype” in human PASMC and PAEC and investigate the role of COX-2 in orchestrating these stiffness-dependent cellular alterations; and 3) to elucidate how stiffness modulates gene expression and to identify key transcription factors involved in stiffness-dependent gene regulation in human PASMC and PAEC.

Overlap: There is no overlap.

Title: Defining the Complex Biology of the miR-130/301 Family in Pulmonary Hypertension (5R01HL124021-05)

Effort: 0.84 Calendar Month (Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Xiao, Lei (lei.xiao@nih.gov)

Performance Period: 01/15/14 – 05/31/19

Funding Amount: direct costs per year

Project Goals: The major goal of this study is to delineate the role of the miR-130/301 family in controlling pulmonary vascular proliferation and vasoconstriction and in promoting pulmonary hypertension.

Specific Aims: The specific aims of this project are 1) to determine the importance of PPAR γ and endothelin-1 for control of pulmonary vasomotor tone by miR-130/301; 2) to determine the importance of PPAR γ and TIMP2 for control of matrix deposition and pulmonary vascular stiffness by miR-130/301; and 3) to define the coordinated actions of the miR-130/301 family members on overall PH manifestation.

Overlap: There is no overlap.

Title: Aspergillus fumigatus Volatile Secondary Metabolite Dynamics for the Identification of Azole-resistant Aspergillosis (5R21AI130669-02)

Effort: 1.2 Calendar Months (Co-Investigator)

Supporting Agency: NIH/NIAID

Grants Officer: Franceschi, Francois J. (francois.franceschi@nih.gov)

Performance Period: 03/01/17 – 02/28/19

Funding Amount: direct costs per year

Project Goals: The major goal of this study is to test the hypothesis that the sesquiterpene secondary metabolite response to triazole antifungal therapy is distinct in azole-susceptible and azole-resistant *A. fumigatus* (ARAF), setting the groundwork for a novel, rapid breath assay that can distinguish patients with ARAF aspergillosis from azole-susceptible invasive aspergillosis, providing an *in vivo* indicator of imminent therapeutic failure, guiding selection of appropriate antifungal therapy, and reducing the extremely high morbidity and mortality associated with ARAF infections. Ultimately, we expect to delineate marked differences in the dynamics of volatile sesquiterpene secondary metabolite release in ARAF vs. azole-susceptible *A. fumigatus*, both *in vitro* and *in vivo*.

Specific Aims: The specific aims of this project are to test the hypothesis that the sesquiterpene secondary metabolite response to triazole antifungal therapy is distinct in azole-susceptible and azole-resistant *A. fumigatus* by (1) comparing the *in vitro* response of ARAF (including the most common cyp51A mutations TR34/L98H, TR46/Y121F/T289A, M220, and G54, and ARAF with phenotypic multi-azole resistance despite wild-type cyp51A) and azole-susceptible *A. fumigatus* strains to azole antifungal therapy and (2) comparing the *in vivo* response of ARAF and azole-susceptible *A. fumigatus* to azole antifungal therapy in breath using a neutropenic murine IA model.

Overlap: There is no overlap.

Title: YAP/TAZ Regulation of TGF- β /BMP Signaling and Vascular Remodeling in PAH (AHA Grant-in-Aid)

Effort: 0.6 Calendar Months (PI)

Supporting Agency: American Heart Association

Grants Officer: McEnany, Rachel (Rachel.McEnany@heart.org)

Performance Period: 07/01/17 – 06/30/20 (NCE)

Funding Amount: total costs per year

Project Goals: The major goal of this study is to investigate the role of the YAP/TAZ pathway in the regulation of TGF- β /BMP signaling in pulmonary arterial hypertension (PAH).

Specific Aims: The specific aims of this project are 1) to investigate the role of YAP and TAZ in regulation of TGF- β /BMP signaling and vascular remodeling in human PASMC and PAEC; and 2) to determine whether inactivation of YAP/TAZ by selective targeting of G α_s -coupled GPCRs enhances BMP signaling, prevents vascular remodeling, and attenuates experimental pulmonary hypertension.

Overlap: There is no overlap.

Title: Acute Lung Injury Group New England Program to Support PETAL Network Research (5U01HL122989-06)

Effort: 0 Calendar Months (Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)

Performance Period: 06/17/14 – 04/30/21

Funding Amount: direct costs per year

Project Goals: The major goal of this project is to develop an innovative and multidisciplinary clinical research consortium in New England to facilitate research by the NHLBI PETAL Network.

Specific Aims: The specific aim of this project is to recruit patients for network ARDS studies and to assist in development and execution of clinical protocols for novel ARDS therapies. This consortium will work together to optimize research processes to screen, enroll, and retain a recruited population of critically ill patients.

Overlap: There is no overlap.

Title: Pulmozyme to Improve COVID-19 ARDS Outcomes

Effort: 0.9 calendar months (Site PI)

Supporting Agency: Boston Children's Hospital (subcontract)

Grants Officer: Clinical Trials Business Office (CTBO), CTBO@childrens.harvard.edu

Performance Period: 05/01/20 – 04/30/21

Funding Amount: direct costs per year

Project Goals: The overall goal 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.

Specific Aims: The specific aims of this project are 1) to conduct a randomized, double-blind placebo controlled study to evaluate the clinical efficacy of rhDNase I in improving clinical outcomes in mechanically ventilated patients; 2) to evaluate the impact of aerosolized rhDNase I on pulmonary injury and systemic inflammation observed in severe COVID-19 pneumonia; and 3) to assess the impact of aerosolized rhDNase I on pulmonary function at 1 year after severe COVID-19 pneumonia.

Overlap: There is no overlap.

CURRENT:

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)

Effort: 1.38 Calendar Months (Site PI)

Supporting Agency: Army Medical Research and Materiel Command

Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)

Performance Period: 09/15/18 – 09/14/22

Funding Amount: direct costs per year

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: Mechanotransduction and YAP/TAZ Signaling in Pulmonary Arterial Hypertension (5R01HL137366)

Effort: 0.95 Calendar Months (PI)

Supporting Agency: NIH/NHLBI

Grants Officer: Fessel, Joshua (josh.fessel@nih.gov)

Performance Period: 01/01/18 – 12/31/21

Funding Amount: direct costs per year

Project Goals: The overall goal is to investigate mechanotransduction and the YAP/TAZ pathway in PAH.

Specific Aims: The specific aims of this project are 1) to investigate the role that YAP/TAZ play in regulating COX-2-dependent prostaglandin production and vascular responses to matrix stiffening in PAH; 2) to examine the mechanisms by

which YAP/TAZ control TGF- β and BMP-dependent Smad signaling, suppress Id1 expression, and regulate cellular growth responses to BMP signaling in PAH; and 3) to determine whether inactivation of YAP/TAZ arrests pulmonary arterial stiffening, attenuates vascular remodeling, and prevents right heart dysfunction in experimental PH.

Overlap: There is no overlap.

Title: TSC2 Signaling in Pulmonary Arterial Hypertension (5R01HL113178)

Effort: 0.47 Calendar Months (Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Fessel, Joshua (josh.fessel@nih.gov)

Performance Period: 04/01/18 – 03/31/22

Funding Amount: direct costs per year

Project Goals: The overall goal is to investigate TSC2 signaling in PAH.

Specific Aims: The specific aims of this project are 1) to critically test the activation status of TSC2 using de-identified lung tissue samples and cultured PAVSMC from idiopathic PAH patients and healthy donors; 2) to determine whether TSC2 deficiency in PAVSMC is induced by increased matrix stiffness and self-supported via Yap/Taz-dependent ECM remodeling; and 3) to evaluate whether epigenetic targeting of TSC2 by Sirt1 activator SRT2104 suppress proliferation and induce apoptosis in vitro in human PAH PAVSMC, reduces excessive ECM production and consequent hyperproliferation of PAEC and PAAF, and reverses or attenuates experimental pulmonary vascular remodeling and PH in rodent SuHx and monocrotaline models.

Overlap: There is no overlap.

Title: Systems biology, endothelial regulation of fibrosis, and pulmonary vascular disease (1R01HL139613)

Effort: 0.12 Calendar Months (Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Xiao, Lei (xiaol@mail.nih.gov)

Performance Period: 01/01/18 – 12/31/21

Funding Amount: direct costs per year

Project Goals: The overall goal is to investigate NEDD9 in regulating pulmonary vascular fibrosis and PAH in vitro and in vivo.

Specific Aims: The specific aims of this project are 1) to prove that NEDD9-Cys18 oxidative modification mediates fibrosis in HPAECs in vitro; 2) to demonstrate that endothelial exosomes mediate a fibrotic pathophenotype in HPASMCs; and 3) to establish that NEDD9 is a lynchpin molecule regulating pulmonary vascular fibrosis and PAH in vivo.

Overlap: There is no overlap.

Title: Rapid, Breath Volatile Metabolite-Based Diagnostic for Ventilator-Associated Pneumonia (VAP) (5R01AI138999)

Effort: 1.2 Calendar Months (Co-Investigator)

Supporting Agency: NIH/NIAID

Grants Officer: Franceschi, Francois J. (francois.franceschi@nih.gov)

Performance Period: 06/01/18 – 05/31/23

Funding Amount: direct costs per year

Project Goals: The overall goal is the development of a breath volatile metabolite platform for the rapid diagnosis of VAP, breath-based identification of its most common causative pathogens, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *E. cloacae*, and *A. baumannii*, and the rapid, real-time, in vivo detection of resistance to antibiotics commonly used for empiric VAP treatment, including methicillin resistance in *S. aureus*, carbapenem and cephalosporin resistance in Enterobacteriaceae, and resistance to multiple antibiotics in *P. aeruginosa* and *A. baumannii*.

Specific Aims: The specific aims of this project are 1) to expand upon *in vivo* breath signatures in murine VAP models to identify early differential breath volatile metabolite responses to antibiotic therapy in susceptible and non-susceptible organisms for each species-antibiotic combination and define robust breath volatile metabolite signatures that differentiate pneumonia; 2) to examine these species-specific volatile breath metabolite signatures in patients with suspected VAP at baseline and at early time points after starting empiric antibiotic therapy, and in ventilated patients with respiratory tract colonization with these organisms; and 3) to optimize GC-DMS peak-finding algorithms for the multiplex, automated identification of the breath volatile metabolite profile of VAP, specific identification of VAP, and within each species-antibiotic combination, the delineation of phenotypic susceptibility vs. non-susceptibility based on early changes in these metabolites with treatment.

Overlap: There is no overlap.

Title: Pulmonary Drug Development

Effort: 2.4 calendar months (Co-Investigator)

Supporting Agency: Bayer, AG

Grants Officer: Seema Basu, ssbasu@PARTNERS.ORG

Performance Period: 09/20/19 – 09/19/24

Funding Amount: direct costs per year

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

Overlap: There is no overlap.

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (1R61HL153011)

Effort: 1.44 Calendar Months in Year 1 (NCE), 3.0 Calendar Months in Years 2-4 (PI)

Supporting Agency: NIH/NHLBI

Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)

Performance Period: 09/15/20 – 08/31/22 (R61); 09/01/22 – 08/31/24 (R33)

Funding Amount: direct costs Year 1 (R61), direct costs Years 2-4 (R33)

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 current 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). Should future grants be awarded such that Dr. Fredenburgh's funded effort exceeds 12 months, Dr. Fredenburgh will request from the NIH an effort reduction to 1.2 CM on 5R01HL137366-03.

PENDING:

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: The inflammasome: A novel biomarker in ALI/ARDS (5 R01 HL112747 04)

Effort: 2.4 Calendar Months (PI)

Supporting Agency: NIH/NHLBI

Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov

Performance Period: 05/15/2012 – 04/30/2017 (NCE)

Funding Amount:

Project Goals: To determine the role of the inflammasome in mediating the effects of administered statins on ARDS.

Specific Aims: (1) To determine gene expression and protein levels of the inflammasome during infection-related ALI/ARDS using prospectively collected blood and banked plasma samples from placebo and statin-treated subjects from the SAILS (Statins for Acutely Injured Lungs from Sepsis) study. (2) To determine the cellular localization of expression of the inflammasome complex and role of inflammasome activation on cellular responses and function, using primary neutrophils and monocytes isolated from prospectively enrolled placebo- and statin-treated SAILS subjects, as well as primary cells isolated from control intensive care unit (ICU) subjects.

Overlap: None

Title: Translational PPG – Carbon Monoxide: Novel Opportunities for Therapy (5 P01 HL108801 05), Clinical Studies Coordination Core

Effort: 1.2 Calendar Months (Core Co-Director)

Supporting Agency: NIH/NHLBI

Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov

Performance Period: 08/15/2011 – 06/30/2017 (NCE)

Funding Amount:

Project Goals: To serve as the Clinical Studies Coordination Core for the translational PPG whose major goal is to translate the findings of cytoprotective properties of carbon monoxide that have been observed in preclinical animal models, to human disease, including a “first in acute lung injury” Phase I carbon monoxide safety trial.

Specific Aims: (1) To identify patients with the systemic inflammatory response syndrome (SIRS), sepsis, and sepsis-induced acute lung injury (ALI); to collect and store plasma, RNA, and primary cells from these patients in a clinical biorepository; as well as to provide biostatistical support for Projects 1-4 for the analysis and interpretation of studies performed using these specimens. (2) To serve as the data coordinating center (DCC) for the Phase 1 first-in-Acute Lung Injury safety study for inhaled CO in sepsis-induced ALI in Project 1 and the proof-of-concept study with collection of muscle biopsies after inhaled CO in Project 2 in the translational PPG. Collection of samples as in Aim 1 will be undertaken pre- and post-CO exposure for distribution to the investigators in Projects 1-4 of the translational PPG. This core will support studies in all projects of the translational PPG.

Overlap: None

Title: Micro-RNAs in Acute Lung Injury (5R01GM115605)
Effort: 2.40 Calendar Months (PI [Multiple PI with Dr. Mark Feinberg])
Supporting Agency: NIH/NIGMS
Grants Officer: Sarah Dunsmore, Ph.D. -- dunsmores@nigms.nih.gov
Performance Period: 08/15/2015 – 05/31/2019

Funding Amount:

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- κ B 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)

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 scale 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 – 04/23/2021

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 – 04/30/21

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 Materiel Command

Grants Officer: Sandy Snyder -- sandy.j.snyder.ctr@mail.mil

Performance Period: 09/15/2018 – 09/14/2022

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 Lung 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 – 08/31/2022 (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 (1R61HL153011-01)

Effort: 0.36 Calendar Months in Year 1, 1.2 Calendar Months in Years 2-4 (Co-Investigator, Co-Director of CCC)

Supporting Agency: NIH/NHLBI

Grants Officer: Lora Reineck, M.D. -- lora.reineck@nih.gov

Performance Period: 09/15/2020 – 08/31/2025

Funding Amount: direct costs year 1

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

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

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

Title: Pulmonary Drug Development

Effort: 2.4 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

None

PREVIOUS/CURRENT/PENDING SUPPORT:

Perrella, Mark A.

PREVIOUS GRANTS (active within past 5 years)

1. “Carbon Monoxide: Novel Opportunities for Therapy”

3.6 calendar months

NIH/NHLBI – 5P01HL108801-05 (Choi/Perrella, PI), Project 3 (Perrella, Project Leader)

Grants Management Specialist: Charmaine Parsad; 301-451-0152; parsadrc@mail.nih.gov

08/15/2011 – 06/30/2017 (NCE)

\$240,749 (Year 5)

Project Goals: Each project will integrate basic aims to determine novel mechanism(s) by which CO mediates its cytoprotection with translational aims focused on proof-of-concept non-human primate and human studies. The synergism between the projects and cores will provide the groundwork to conduct a Phase II inhaled CO intervention trial in ALI during Cycle II of this translational P01 application.

Specific Aims: The specific aims of Project 3 are to 1) investigate the biological response of MSC administration to mice after the onset of microbial sepsis; 2) condition MSCs with CO, a downstream product of the cytoprotective enzyme HO-1, and investigate their biological response in mice with sepsis; 3) decipher the mechanisms responsible for the enhanced response of MSCs, after exposure to CO, in murine sepsis; and 4) advance the understanding of the human immune response to MSC therapy in sepsis using “humanized” mice and *in vitro* analyses.

Overlap: none

2. “The Functional Consequences of the 17q12 Asthma Susceptibility Locus”

0.36 calendar months

NIH/NHLBI – 5R01 HL117837-03 (Raby, PI)

Program Official: Weiniu Gan; ganw2@nhlbi.nih.gov

07/01/2015 – 06/30/2019

per year

Project Goals: The overall goal of this proposal is to conclusively identify the gene that is responsible for genetic associations observed with asthma on chromosome 17q12 and to characterize its molecular, cellular, metabolic and phenotypic consequences.

Specific Aims: In Specific Aim 1, we will study inducible transgenic mice generated in our lab that conditionally over express ORMDL3 or GSDMB in bronchial epithelium. In Specific Aim 2, we will experimentally assess (via *in vitro* knockdown and over expression studies) the independent cellular consequences of ORMDL3 and GSDMB expression in human bronchial epithelial cells derived from individuals homozygous for the risk and protective 17q12 haplotypes. In Specific Aim 3, we will study the relationship of 17q12 haplotype with sphingolipid metabolism. Overlap: none

3. “Phase 2 Study of Safety, Tolerability, and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease”

1.2 calendar months

Investigator Initiated Clinical Trial, Rosas / Roche (Goldberg, PI; Perrella, Medical Monitor)

04/01/2016 – 03/31/2021

total costs

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

4. “Regulation of Neutrophil Function by Mesenchymal Stromal Cells During Sepsis”

2.74 calendar months

NIH/NIGMS – 5R01 GM118456-04 (Perrella, PI)

Grants Management Specialist: Anna Hahn; 301-594-5506, hahnann@mail.nih.gov

05/10/2016 – 02/28/2021

(per year)

Project Goals: The overall goal is to investigate the regulation of neutrophil function by mesenchymal stromal cells during sepsis.

Specific Aims: The specific aims of the project are 1) to investigate the importance of SDF-1 for the therapeutic effects of MSCs in an experimental mouse model of sepsis, using cecal ligation and puncture (CLP); 2) to explore the interaction between MSCs and neutrophils during experimental sepsis in mice, and elucidate the role of MSC-derived SDF-1 to improve neutrophil function; and 3) to determine whether MSCs can rescue human neutrophil dysfunction in cells harvested from patients with sepsis, and elucidate the role of SDF-1 in this MSC response.

Overlap: none

ACTIVE GRANTS

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

2.4 calendar months

NIH/NIAID – 5U01AI138318 (Lederer, PI; Perrella, co-PI)

Scientific Research Contact: Carmen Rios, PhD; Carmen.Rios@nih.gov

04/01/2018 – 03/31/2023

per year

The goal of the project are: 1) to test the hypothesis that pre-conditioning MSCs by CpG-ODN stimulation will enhance their beneficial effects on anti-microbial immune function and hematopoietic system recovery after radiation exposure; 2) to determine the biological effects of CpG-ODN stimulation on MSCs phenotype and function; and 3) to interrogate mechanisms responsible for protective effects of CpG-MSCs on radiation injury and recovery.

Overlap: none

2. “Systems Biology of Airway Disease”

0.6 calendar months

NIH/NHLBI – 5 P01 HL132825-05 (Weiss, PI)

Grants Management Specialist: Suzanne White; whitesa@nhlbi.nih.gov

09/01/2016 – 07/31/2022

per year

Functional Genomics Core (Perrella, Co-Investigator)

The overarching goal of the program project, “Systems Biology of Airway Disease”, is to identify common molecular determinants and pathways for asthma and COPD. These determinants will be identified through the use of a diverse array of molecular data — DNA sequencing and genomewide SNP data (Project 1), RNA-sequencing and expression data (Project 2), methylation sequencing and miRNA sequencing data (Project 3). The Functional Genomics Core will explore the functional importance of these molecular determinants and pathways for the development of asthma and COPD.

Overlap: none

3. “A Phase 2 Study of Inhaled CO for the Treatment of ARDS”

1.2 calendar months

Department of Defense (DoD) - W81XWH1810667 (Choi, PI; Perrella, Co-Investigator)

Grants Officer: Sandy Snyder; sandy.j.snyder.ctr@mail.mil

09/15/2018 – 09/14/2022

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

4. “Mesenchymal Stromal Cells, Autophagy, and the Host Response to Systemic Bacterial Infection”

2.4 calendar months

NIH/NIGMS – 1 R01 GM136804 (Perrella, PI)

Grants Management Specialist: Anna Hahn, hahnann@mail.nih.gov

04/01/2020 – 01/31/2024

per year

The goals of the project are 1) to decipher the importance of the autophagy pathway, for enhanced MSC function during sepsis, after CO pre-conditioning of MSCs *ex vivo*; 2) to determine the role of extracellular vesicles (EVs) in the paracrine actions of MSCs pre-conditioned with CO, and investigate the importance of autophagy in this response; and 3) to determine whether *ex vivo* pre-conditioning of MSCs with CO improves the outcome of autophagy protein deficient mice during sepsis.

Overlap: none

5. “Pulmonary Drug Development”

1.2 calendar months

Bayer, AG (Levy, PI; Perrella, Co-Investigator)

Contact: Seema Basu, ssbasu@partners.org

09/20/2019 – 09/19/2024

per year

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

Overlap: none

PENDING GRANTS

1. “A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS”

1.2 calendar months in Years 2-4 in the R33 Phase of the Award

NIH/NHLBI – 1 R61HL153011-01 (Choi, Fredenburgh PI; Perrella, Co-Investigator)

Grants Officer: Lora Reineck, lora.reineck@nih.gov

09/15/2020 – 08/31/2022 (R61); 09/01/2022 – 08/31/2025 (R33)

Year 1 (R61), Years 2-4 (R33)

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

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

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

PREVIOUS/CURRENT/PENDING SUPPORT:

EL-CHEMALY, SOUHEIL

PREVIOUS:

Title: Targeting Autophagy for the Treatment of TSC and LAM (W81XWH-12-1-0578)

Effort: 0 Calendar Months (Co-I)

Supporting Agency: U.S. Army Medical Research Acquisition Activity

Grants Officer: Athansiou, Meropi (meropi.athanasiou.civ@mail.mil)

Performance Period: 09/30/2012-09/29/2017 (NCE)

Funding Amount: direct costs per year

Project Goals: The goals of this phase I clinical trial are 1) To investigate whether, in LAM patients, the combination of sirolimus and hydroxychloroquine is safe and well tolerated; 2) To investigate whether, in LAM patients, 6 months of combination therapy with sirolimus and hydroxychloroquine results in improvement of indicators of disease, and whether the gains are sustained after stopping therapy; and 3) To investigate the potential role of a LAM-specific peripheral blood signature to predict rates of disease progression and determine responsiveness to combination therapy.

Specific Aims: **Aim 1.** To investigate whether, in LAM patients, the combination of sirolimus and hydroxychloroquine is safe and well tolerated. **Aim 2.** To investigate whether, in LAM patients, 6 months of combination therapy with sirolimus and hydroxychloroquine results in improvement of indicators of disease, and whether the gains are sustained after stopping therapy. **Aim 3.** To investigate the potential role of a LAM-specific peripheral blood signature to predict rates of disease progression and determine responsiveness to combination therapy.

Overlap: There is no overlap.

Title: Rare Diseases Clinical Research Network/Rare Lung Diseases Consortium (5U54HL127672-04)

Effort: 0.1 Calendar Months (Co-I)

Supporting Agency: NIH/NHLBI/NCATS

Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)

Performance Period: 08/01/2015-07/31/2018

Funding Amount: direct costs per year

Project Goals: This grant aims to study rare lung diseases, including Lymphangioleiomyomatosis (LAM), Pulmonary Alveolar Proteinosis (PAP), and Hermansky-Pudlak Syndrome (HPS), as well as other rare lung diseases. This consortium includes longitudinal and treatment studies, development of biomarkers and novel diagnostics, and outcomes measures, as well pilot project and training programs.

Specific Aims: The proposed Specific Aims include 1) establish a Consortium focused to Lymphangioleiomyomatosis (LAM), Pulmonary Alveolar Proteinosis (PAP), and Hermansky-Pudlak Syndrome (HPS), 2) conduct longitudinal and therapeutic clinical studies related to LAM, PAP, and HPS at abroad network of rare lung disease clinical centers established initially via LAM clinics, 3) conduct of a Pilot and Demonstration program for the development and evaluation of novel diagnostics, therapeutics, and outcome measures for these and additional 'on-deck' rare lung diseases, 4) provide clinical research training at RLDC clinical centers and attract new investigators to the field, and 5) develop rare lung disease educational materials for patients, medical providers, and the public.

Overlap: There is no overlap.

Title: COLA: A Pilot Clinical Trial of COX-2 inhibition in LAM and TSC (W81XWH-15-1-0511)

Effort: 1.44 Calendar Months (Co-I)

Supporting Agency: U.S. Army Medical Research Acquisition Activity

Grants Officer: Athansiou, Meropi (meropi.athanasiou.civ@mail.mil)

Performance Period: 09/15/2015-09/14/2018 (NCE)

Funding Amount: direct costs per year

Project Goals: The goals of this study are 1) To investigate whether, in LAM patients, celecoxib is safe and well tolerated; 2) To investigate whether, in LAM patients, celecoxib treatment for 6 months results in improvement in LAM disease indicators; and 3) To investigate the potential value of a novel biomarker of LAM, quantitative measurement of TSC2 mutant LAM cells per ml of blood, to assess disease severity.

Specific Aims: **Aim 1:** To perform a clinical trial of the selective COX-2 inhibitor celecoxib for lymphangioleiomyomatosis (LAM). **Aim 2:** To investigate whether, in LAM patients, celecoxib treatment for 6 months

results in improvement in LAM disease indicators. **Aim 3:** To investigate the potential value of a novel biomarker of LAM, quantitative assessment of TSC2 mutation in circulating LAM cells, to assess disease severity.

Overlap: There is no overlap.

Title: Clinical Genetics and Screening for Pulmonary Fibrosis (5R01HL130974-04)

Effort: 0.6 Calendar Months (Co-I)

Supporting Agency: NIH/NHLBI

Grants Officer: Harabin, Andrea L. (andrea.harabin@nih.gov)

Performance Period: 01/01/2016-12/31/2020

Funding Amount: direct costs per year

Project Goals: The goal of this proposal is to demonstrate the value of genetic testing for diagnostic and prognostic evaluation of patients with, or at risk for IPF. Recent studies also demonstrate that genetic testing may be a critical factor that can help guide early detection. We hypothesize that specific, known genetic variants confer variable prognosis in patients with pulmonary fibrosis (PF), and that targeted genetic testing will aid in patient counseling, early disease detection, and ultimately, earlier initiation of medical therapy.

Specific Aims: To assess these hypotheses we propose to address the following specific aims: Aim 1) Does targeted genetic testing aid in the diagnostic and prognostic evaluation of patients with pulmonary fibrosis? Aim 2) Does targeted genetic testing aid in early detection, and prognostication of populations at-risk for pulmonary fibrosis? and Aim 3) We will assess the psychosocial impact of genetic testing groups at-risk for pulmonary fibrosis.

Overlap: There is no overlap.

Title: LAMP: The LAM Microbiome Project (W81XWH-17-1-0469)

Effort: 1.2 Calendar Months (PI)

Supporting Agency: U.S. Army Medical Research Acquisition Activity

Grants Officer: Athansiou, Meropi (meropi.athanasiou.civ@mail.mil)

Performance Period: 09/15/2017-09/14/2021

Funding Amount: direct costs per year

Project Goals: The goals of this study are 1) To investigate the LAM microbiome in early disease and 2) To investigate the LAM microbiome in LAM lung explanted at the time of transplant. The major goal is to establish the microbiome as a biomarker of disease progression or a therapeutic target.

Specific Aims: **Aim 1:** To define the respiratory tract microbiome in women with LAM with early lung disease.

Aim 2: To define the lung microbiome of explanted LAM lung.

Overlap: There is no overlap.

CURRENT:

Title: Lymphatics and Lung Allograft Rejection (5R01HL130275)

Effort: 3.6 Calendar Months (PI)

Supporting Agency: NIH/NHLBI

Grants Officer: Craig, Matt (matt.craig@nih.gov)

Performance Period: 07/01/2016-04/30/2022

Funding Amount: direct costs per year

Project Goals: The goals of this proposal are to understand the functions of the lymphatic vasculature in acute lung allograft rejection.

Specific Aims: **Aim 1.** To identify the origin of lymphatic endothelial cells in lymphatic vessel regeneration after lung transplantation; **Aim 2.** To determine mechanisms whereby lymphangiogenesis protects against lung allograft rejection;

Aim 3. To demonstrate that lymphatic specific changes in lung tissue and peripheral blood can predict acute lung rejection and response to therapy.

Overlap: There is no overlap.

Title: The Molecular and Genetic Pathogenesis of LAM (5U01HL131022)

Effort: 1.2 Calendar Months (Co-PI)

Supporting Agency: NIH/NHLBI

Grants Officer: Reineck, Lora A. (lora.reineck@nih.gov)

Performance Period: 09/21/2016-02/28/2025

Funding Amount: direct costs per year

Project Goals: This U01 brings together a unique team of leaders in LAM research to address key unanswered questions with high clinical impact. First, what are the fundamental mechanisms leading to lymphangiogenesis in LAM? Second, can circulating LAM cell burden be quantitated through "next generation" sequencing and used as a biomarker of LAM? Third, will finer dissection of the genetic basis of sporadic LAM reveal generalized low-level TSC2 mosaicism? Fourth, can biomarkers including VEGF-D and microRNA be used to develop personalized strategies for sirolimus dosing?

Specific Aims: The major goals of this project are: 1) to use freshly isolated circulating LAM cells and monocytic cells collected from serum of LAM patients at the NIH Clinical Center to determine the specific cell type and the cellular mechanism of VEGF-D overexpression in LAM, 2) to use next generation sequencing (NGS) to identify TSC1/TSC2 mutations in circulating LAM cells, and 3) to correlate the effect of sirolimus on serum microRNA, circulating LAM cells, VEGF-D and other lymphangiogenic factors, and indicators of mTORC1 activity, leading to the preliminary design of a combinatorial biomarker signature of sirolimus efficacy in LAM and enabling future studies of personalized dosing.

Overlap: There is no overlap.

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)

Effort: 0.6 Calendar Months (Co-Investigator)

Supporting Agency: Army Medical Research and Materiel Command

Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)

Performance Period: 09/15/2018-09/14/2022

Funding Amount: direct cost per year

Project Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.

Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

Overlap: There is no overlap.

Title: Targeting the Angiotensin Receptor in TSC (W81XWH1910250)

Effort: 2.4 Calendar Months (PI)

Supporting Agency: DOD

Grants Officer: Ebony S. Simmons (ebony.s.simmons.civ@mail.mil)

Performance Period: 06/01/2019-05/31/2022

Funding Amount: direct costs per year

Project Goals: The major goals of this project are to understand the role of AGTR1 in TSC2-deficient cell death.

Specific Aims: **Aim 1:** To investigate the role of AGTR1 inhibition in TSC2-deficient cell growth in vivo. **Aim 2:** To investigate AGTR1-dependent mechanisms of TSC2-deficient cell death in vitro. **Aim 3:** To investigate klotho-dependent TSC2-null cell death in vivo and to identify a klotho-dependent signature of LAM and TSC.

Overlap: There is no overlap.

Title: Angiotensin II Type 1 Receptor Trafficking in Lung Fibroblasts and Its Role in HPS Lung Fibrosis

Effort: 0.12 Calendar Months (PI)

Supporting Agency: American Thoracic Society

Grants Officer: Erin Nebel, emnebel@thoracic.org

Performance Period: 01/15/2018-01/14/2022

Funding Amount: direct costs per year

Project Goals: Our goal is to show that a group of drugs that exist on the market -used for blood pressure can reverse the changes that we are seeing in the HPS1 fibroblast and the resulting effects on other lung cell types. The overall goal is to provide reasoning and scientific justification to use these drugs first in mice and perhaps later in patients with HPS1.

Overlap: There is no overlap.

Title: Pulmonary Drug Development

Effort: 2.4 calendar months (Co-Investigator)

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: There is no overlap.

PENDING:

Title: Distinct and Overlapping Pathways of Fibrosis and Emphysema in Cigarette Smokers (2P01HL114501-06A1)

Effort: 1.2 calendar months (Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Antonello Punturieri, punturiera@nhlbi.nih.gov

Performance Period: 06/10/2021-05/31/2026

Funding Amount: per year

Project Goals: The goal of this study is to identify the common and divergent biologic processes that lead to chronic parenchymal lung disease in smokers.

Overlap: There is no overlap.

Title: Clinical Genetics and Screening for Pulmonary Fibrosis (2R01HL130974-05A1)

Effort: 1.2 calendar months (Co-Investigator)

Supporting Agency: NIH/NHLBI

Grants Officer: Nina Hall, hallnn@mail.nih.gov

Performance Period: 12/01/2021-11/30/2026

Funding Amount: per year

Project Goals: The goals of this proposal are to identify the role of clinical genetic testing in patients with clinically identified pulmonary fibrosis, and to determine the role of genetics and early screening in first-degree relatives of patients with pulmonary fibrosis. Positive results from these studies will transform care for patients with, or in those suspected to have IPF, and will set the stage for subsequent clinical trials to prospectively evaluate the efficacy of pre-clinical screening and early treatment for IPF.

Overlap: There is no overlap.

PREVIOUS/CURRENT/PENDING SUPPORT:

HOU, PETER

PREVIOUS:

Title: Late Cardiovascular Consequences of Septic Shock and ARRA Supplement

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH/NIGMS R01 GM097471 (Yende)

Grants Officer: Sarah Dunsmore (sarah.dunsmore@nih.gov)

Performance Period: 06/01/2012-05/31/2017

Funding Amount: (per participant enrolled, 47 participants enrolled) and

Project Goals: To follow and examine patients who were enrolled in the ProCESS clinical study or who had a clinical diagnosis of sepsis for the effect of Protocolized resuscitation on the development of AKI, the recovery of kidney function, late cardiovascular events, quality of life, and long-term mortality.

Specific Aims: (1) To test the hypothesis that protocolized resuscitation prevents or lessens severity or duration of AKI. (2) To determine which pathophysiological derangements, in combination or individually, are associated with the development of AKI and CVD. (3) To determine whether biomarkers can predict AKI and recovery from AKI in the setting of sepsis.

Overlap: There is no overlap.

Title: Acute Lung Injury Group New England (ALIGN) Clinical Center Program to Support PETAL Network

Effort: 0.24 calendar month (Co-Lead)

Supporting Agency: NIH/NHLBI U01 HL122989 (Steingrub)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 06/17/2014-04/30/2021

Funding Amount:

Project Goals: To develop and conduct at least 3-5 randomized controlled clinical trials to prevent, treat, and/or improve the outcome of adult patients with, or at risk for, ALI or the acute respiratory distress syndrome (ARDS).

Specific Aims: Each CC was expected to enroll 220 patients over 5.5 years.

Overlap: There is no overlap.

Title: Procalcitonin Antibiotic Consensus Trial (ProACT)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH/NIGMS R01 GM101197 (Huang)

Grants Officer: Sarah Dunsmore (sarah.dunsmore@nih.gov)

Performance Period: 08/01/2014-07/31/2017

Funding Amount: (per participant enrolled, 205 participants enrolled)

Project Goals: To target emergency department (ED) patients with clinically diagnosed lower respiratory tract infection (LRTI) and test the effects of implementation of a procalcitonin antibiotic guideline for LRTI.

Specific Aims: (1) To determine the effect of implementation of a procalcitonin guideline on antibiotic exposure in clinically diagnosed LRTI. (2) To determine the effect of implementation of a procalcitonin guideline on a 30-day combined adverse outcome.

Overlap: There is no overlap.

Title: Rapid Administration of Carnitine in sEpsis (RACE) Trial

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH/NIGMS R01 GM103799 (Jones)

Grants Officer: Sarah Dunsmore (sarah.dunsmore@nih.gov)

Performance Period: 10/01/2014-05/31/2018 (5 participants enrolled)

Funding Amount: (5 participants enrolled)

Project Goals: To conduct an efficacy and safety trial of L-carnitine as a novel adjunctive treatment for patients in septic shock.

Specific Aims: (1) To test if intravenous L-carnitine reduces cumulative organ failure in septic shock. (2) To test if L-carnitine improves blood flow in the sublingual microvasculature during septic shock.

Overlap: There is no overlap.

Title: A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: La Jolla Pharmaceutical Company, Inc. (Tidmarsh)

Grants Officer: Dan Yaeger (858-207-4264)

Performance Period: 03/30/2015-02/19/2017

Funding Amount: (1 participant enrolled)

Project Goals: To compare the effect of LJPC-501 infusion on mean arterial pressure in patients with CRH.

Specific Aims: (1) To compare change in Sequential Organ Failure Assessment (SOFA) scores. (2) To establish the safety and tolerability of LJPC-501 and compare to placebo in patients with CRH.

Overlap: There is no overlap.

Title: Reevaluation Of Systemic Early neuromuscular blockade (ROSE)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH/NHLBI U01 HL123009 (Steingrub)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 11/16/2015-04/30/2018

Funding Amount: (per participant enrolled, 16 participants enrolled)

Project Goals: To assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate-severe ARDS in comparison to a control group with no routine early neuromuscular blockade.

Specific Aims: To assess if early neuromuscular blockade will improve mortality prior to discharge home before day 90, in patients with moderate-severe ARDS.

Overlap: There is no overlap.

Title: LOw Tidal volume Universal Support: Feasibility of RecrUitment for Interventional Trial (LOTUS FRUIT)

Effort: 0.24 calendar month (Protocol Study Co-Chair)

Supporting Agency: NIH U01HL123009, CCC for NHLBI Prevention and Early Treatment of Acute Lung Injury PETAL Network (MGH)

Grants Officer: Andrea Harabin (andrea.harabin@nih.gov)

Performance Period: 05/01/2016-04/30/2017

Funding Amount:

Project Goals: To chair the assessment of hospital mechanical ventilation practices.

Specific Aims: (1) To inform the design and plan for a pragmatic interventional cluster randomized control trial of low tidal volume ventilation in the emergency department and intensive care unit. (2) To determine the feasibility of data collection for patients with acute respiratory failure in a pragmatic trial.

Overlap: There is no overlap.

Title: LOw Tidal volume Universal Support: Feasibility of RecrUitment for Interventional Trial (LOTUS FRUIT)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH HL123009 (Steingrub)

Grants Officer: Andrea Harabin (andrea.harabin@nih.gov)

Performance Period: 06/22/2016-04/30/2017

Funding Amount: (53 participants enrolled)

Project Goals: To assess hospital mechanical ventilation practices.

Specific Aims: (1) To inform the design and plan for a pragmatic interventional cluster randomized control trial of low tidal volume ventilation in the emergency department and intensive care unit. (2) To determine the feasibility of data collection for patients with acute respiratory failure in a pragmatic trial.

Overlap: There is no overlap.

Title: Effect of randomization to neuromuscular blockade on physical functional impairment and recovery in ARDS (PRIMROSE)

Effort: 1.2 calendar months (Site PI)

Supporting Agency: NIH R01HL132232-02 (Hough)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 08/16/2016-06/30/2019

Funding Amount: (5 participants enrolled)

Project Goals: To conduct a prospective longitudinal cohort study nested within the ROSE RCT, and extensively leveraging the ROSE RCT's patients screening, enrollment, and follow-up infrastructure and to use stage-appropriate multi-modal assessments of neuromuscular function to identify the effect of randomization to NMB.

Specific Aims: To determine the effect of NMB (1) on the early development of ICU-acquired neuromuscular dysfunction, assessed primarily via nerve conduction study in the ICU; (2) on muscle function and strength at hospital discharge, assessed primarily using standardized handgrip dynamometry; and, (3) on physical recovery and healthcare utilization 6 and 12 months after the development of severe ARDS, assessed primarily using the Short Physical Performance Battery and the Medical Expenditure Panel Survey questionnaire.

Overlap: There is no overlap.

Title: Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH HL123009 (Steingrub)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 12/01/2016-04/30/2019

Funding Amount: (71 participants enrolled)

Project Goals: To assess the efficacy and safety of early administration of vitamin D₃ (cholecalciferol) in reducing mortality and morbidity for vitamin D deficient patients at high risk for ARDS and mortality.

Specific Aims: To determine if early administration of vitamin D₃ (cholecalciferol) will improve all-cause, all-location mortality to day 90 in vitamin D deficient patients at high risk for ARDS and mortality.

Overlap: There is no overlap.

Title: Reverse Engineering Host Resilience

Effort: 0.12 calendar month (Site PI)

Supporting Agency: Defense Advances Research Projects Agency (DARPA) – Presidents and Fellows of Harvard College (Harvard) – Beth Israel Deaconess Medical Center (BIDMC)

Grants Officer: Rachel Talentino (rachel_talentino@harvard.edu)

Performance Period: 03/03/2017-09/02/2018

Funding Amount: (100 participants enrolled)

Project Goals: To develop an assay that offers a rapid, simple, sensitive and specific method for diagnosing infections.

Specific Aims: To recruit patients with sepsis as well as non-infected control subjects for participation in the study, obtaining blood samples and delivering them to the Wyss Institute for analysis, and collecting and recording the key data elements that characterize the corresponding clinical phenotype and outcomes for each study participant.

Overlap: There is no overlap.

Title: LJ501-EAP01 Expanded Access for LJPC-501

Effort: 0.12 calendar month (Site PI)

Supporting Agency: La Jolla Pharmaceutical Company, Inc. (Chawla)

Grants Officer: Dennis Mulroy (Dennis.Mulroy@ljpc.com)

Performance Period: 09/19/2017-02/14/2018

Funding Amount: (1 participant enrolled)

Project Goals: To provide access to LJPC-501 for distributive shock patients who remain hypotensive despite receiving fluid and vasopressor therapy while the drug is in mass production.

Specific Aim: To continue the safety assessment of LJPC-501 after FDA approval.

Overlap: There is no overlap.

Title: PETAL Network: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH HL123009 (Steingrub)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 11/01/2017-04/30/2020

Funding Amount: (9 participants enrolled)

Project Goals: To assess the effect of the combination of vasopressor and fluid therapies in sepsis-induced hypotension on patient outcome.

Specific Aims: To determine the impact of a restrictive fluid strategy (vasopressors first followed by rescue fluids) as compared to a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

Overlap: There is no overlap.

Title: Ascorbic Acid, Hydrocortisone, and Thiamine in Sepsis and Septic Shock – A Randomized, Double-Blind, Placebo-Controlled Trial (ACTS)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: Good Ventures – BIDMC (Donnino)

Grants Officer: Chris Somerville and Heather Youngs

Performance Period: 06/01/2018-05/31/2019

Funding Amount: (16 participants enrolled)

Project Goals: To assess the effect of a metabolic resuscitation bundle of therapies in septic shock on patient outcomes.

Specific Aims: To determine the impact of vitamin C, hydrocortisone, and vitamin B1 vs. placebo on organ injury and mortality in participants with sepsis and septic shock.

Overlap: There is no overlap.

Title: Long-term Brain Outcomes in Vitamin D deficient patients (VIOLET-BUD)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH HL141567 (Han)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 09/05/2018-08/31/2020

Funding Amount: (5 participants enrolled)

Project Goals: To perform comprehensive neuropsychological (cognitive) evaluations in participants enrolled in the VIOLET trial.

Specific Aims: To determine if early administration of a single high-dose (540,000 IU) oral vitamin D3 (cholecalciferol) treatment improves 12-month global cognition and executive function as determined by comprehensive neuropsychological testing in 140 critically ill patients with Vitamin D deficiency at enrollment.

Overlap: There is no overlap.

Title: DIStinguish Respiratory Underlying Pathogen associaTed host response in Acute Respiratory Infection: An Evaluation of FebriDx® POC Test (FebriDx® DISRUPT ARI Trial)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: Rapid Pathogen Screening, Inc. Protocol 13-0830 (Shapiro)

Grants Officer: Annie Bell (annie.bell@lumosdiagnostics.com)

Performance Period: 4/30/2019-10/30/2020

Funding Amount: per participant enrolled (40 participants enrolled)

Project Goals: To evaluate a new point of care rapid diagnostic test called FebriDx[®], a test that identifies an immune response to a viral and/or bacterial cause of a community acquired respiratory infection.

Specific Aims: To determine performance characteristics of the FebriDx[®] test in predicting viral or bacterial infection etiology among febrile (observed or reported) patients presenting the emergency department, urgent care centers or primary care offices with suspected acute respiratory tract infection.

Overlap: There is no overlap.

Title: Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease trial (ORCHID)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH HL123009 (Steingrub)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 04/15/2020-07/23/2020

Funding Amount: (9 participants enrolled)

Project Goals: To determine whether hydroxychloroquine is an efficacious treatment for adults hospitalized with COVID-19.

Specific Aims: To compare the effect of hydroxychloroquine versus placebo on clinical outcomes, measured using the COVID Ordinal Outcomes Scale at Day 15, among adults with COVID-19 requiring hospitalization.

Overlap: There is no overlap.

Title: Mesenchymal Stem Cells for the Treatment of Moderate to Severe COVID-19 Acute Respiratory Distress Syndrome

Effort: 0.12 calendar month (Site PI)

Supporting Agency: NIH/NHLBI

Grants Officer: Tawana McKeither

Performance Period: 03/01/2020-02/28/2021

Funding Amount: per participant enrolled (1 participant enrolled)

Project Goals: To evaluate the efficacy and safety of the addition of the mesenchymal stromal cell (MSC) remestemcel-L[®] to standard of care in patients with acute respiratory distress syndrome (ARDS) due to COVID-19.

Overlap: There is no overlap.

Title: A Phase 2, randomized, placebo-controlled, participant and investigator blinded, multi-center study to assess efficacy and safety of MAS825 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function

Effort: 0.12 calendar month (Site PI)

Supporting Agency: Novartis Pharmaceuticals

Grants Officer: Maureen Watson

Performance Period: 05/18/2020-03/31/2021

Funding Amount: per participant enrolled (1 participant enrolled)

Project Goals: To evaluate the efficacy and safety of MAS825 in addition to current standard of care (SoC) compared with Placebo and SoC in controlling the inflammatory syndrome and resultant acute respiratory distress syndrome (ARDS) in hospitalized patients presenting with COVID-19 pneumonia and impaired respiratory function.

Specific Aims: To evaluate the effect of MAS825, compared with placebo, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Overlap: There is no overlap.

Title: A Multi-Center, Adaptive, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Gimsilumab in Participants With Lung Injury or Acute Respiratory Distress Syndrome (ARDS) Secondary to Coronavirus Disease 2019 (COVID-19)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: Kivenant

Grants Officer: Joe Bishop

Performance Period: 06/15/2020-06/14/2021

Funding Amount: per participant enrolled

Project Goals: To evaluate the impact of intravenous (IV) treatment with gimsilumab on mortality in participants with lung injury or ARDS secondary to COVID-19.

Overlap: There is no overlap.

Title: ACTIV-1 IM: Randomized Master Protocol for Immune Modulators for Treating COVID-19

Effort: 0.6 calendar month (Site PI)

Supporting Agency: Duke University

Grants Officer: Joshua A. Lance, J.D. (joshua.lance@duke.edu)

Performance Period: 8/17/2020 – 9/01/2021

Funding Amount: per participant enrolled

Project Goals: To speed development of the most promising treatments and vaccines.

Specific Aims: To evaluate immunomodulatory therapy as additions to standard of care for hospitalized COVID patients with moderate to severe infection. Currently, we are evaluating infliximab, abatacept and cenicriviroc, with the primary endpoint being time to recovery at 29 days.

Overlap: There is no overlap.

CURRENT:

Title: ACTIV-IV COVID-19 Outpatient Thrombosis Prevention Trial

Effort: 0.6 calendar month (Site PI)

Supporting Agency: PAREXEL International, LLC/RTI/NHLBI

Grants Officer: Frank Sciurba, MD (sciurbafc@upmc.edu)

Performance Period: 2/5/2021 – 2/4/2022

Funding Amount: per participant enrolled (27 participants enrolled)

Project Goals: To evaluate the efficacy and safety of antithrombotic strategies in COVID-19 adults not requiring hospitalization at time of diagnosis.

Specific Aims: To compare the effects of treatment in COVID-19 patients not requiring hospitalization at time of diagnosis (WHO COVID-19 ordinal score 1-3) with (i) prophylactic dose anticoagulation; with (ii) therapeutic dose anticoagulation; with (iii) antiplatelet therapy; and with (iv) placebo relative to each other on the primary composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days among the study population of non-hospitalized COVID-19 patients aged > 40 years.

Overlap: There is no overlap.

Title: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)

Effort: 0.24 calendar month (Co-Investigator)

Supporting Agency: Army Medical Research and Materiel Command (Choi)

Grants Officer: Sandy Snyder (sandy.j.snyder.ctr@mail.mil)

Performance Period: 09/15/2018-09/14/2022

Funding Amount:

Project Goals: To evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.

Specific Aims: 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.

Overlap: There is no overlap.

Title: A Randomized Double Blind, Placebo-Controlled Study of Auxora for the Treatment of Severe COVID-19 Pneumonia (CARDEA)

Effort: 0.12 calendar month (Site PI)

Supporting Agency: CalciMedia, Inc.

Grants Officer: Michael Dunn

Performance Period: 08/06/2020-08/05/2022

Funding Amount: per participant enrolled (20 participants enrolled)

Project Goals: To assess the clinical efficacy of Auxora in patients with severe COVID-19 pneumonia.

Overlap: There is no overlap.

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R61HL153011-01)

Effort: 0.24 calendar month in Years 2-4 in the R33 Phase of the Award (Co-Investigator)

Supporting Agency: NIH/NHLBI (Fredenburgh)

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 09/15/2020-08/31/2021 (R61); 09/01/2021-08/31/2024 (R33)

Funding Amount:

Project Goals: To investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.

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

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

Title: PReventing Emerging infections through Vaccine EffectiveNess Testing - COVID (Project PREVENT)

Effort: 0.6 calendar month (Site PI)

Supporting Agency: Olive View/UCLA Education and Research Institute, Inc./CDC

Grants Officer: Anusha Krishnadasan (idnet@ucla.edu)

Performance Period: 11/15/2020 – 12/31/2021

Funding Amount: (152 participants enrolled)

Project Goals: To continue *EMERGENCY* ID NET study collaboration with the CDC to conduct ongoing investigations of emerging infectious diseases and common acute infections presenting to EDs in the U.S.

Specific Aims: 1.) identifying emerging and prevalent infections among ED patients; 2) developing study protocols, procedures, consent documents, case report forms, and other data collection materials; 3) obtaining necessary approvals to conduct the research from Institutional Review Boards (IRB); 4) implementing the studies through enrollment and follow-up of ED patients; 5) managing data collection activities, including specimen collection and shipment, 6) constructing data entry modules and managing data entry with quality and accuracy checks; and 7) analyzing data, summarizing results, and reporting our study findings in peer-reviewed publications and at scientific conferences.

Overlap: There is no overlap.

Title: CONNECTS Master Protocol for Clinical Trials targeting macro-, micro-immuno-thrombosis, vascular hyperinflammation, and hypercoagulability and renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19 (ACTIV-4 Host Tissue)

Effort: 0.6 calendar month (Site PI)

Supporting Agency: Vanderbilt University Medical Center/NHLBI

Grants Officer: Aubrey Mann, JD (aubrey.t.mann@vumc.org)

Performance Period: 3/1/2021 – 5/31/2022

Funding Amount: per participant enrolled

Project Goals: To test novel experimental COVID therapies affecting host response.

Specific Aims: To target the renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19.

Overlap: There is no overlap.

Title:

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Varespladib in Patients Hospitalized with Severe COVID-19 Caused by SARS-CoV-2 (STAIRS)

Effort: 0.6 calendar month (Site PI)

Supporting Agency: Premier Research International, LLC

Grants Officer: Margie Mullen (margie.mullen@premier-research.com)

Performance Period: 9/7/2021 – 9/6/2026

Funding Amount: per participant enrolled

Project Goals: To study the drug Varespladib to prevent deterioration of pulmonary function associated with SARS -CoV-2 infection.

Specific Aims: To test varespladib as a novel mechanism of action to mitigate sPLA2 over-activity and prevent surfactant degradation.

Overlap: There is no overlap.

PREVIOUS/CURRENT/PENDING SUPPORT:

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.

CURRENT:

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: A Phase II Study of Inhaled Carbon Monoxide for the Treatment of ARDS (W81XWH1810667)

Effort: No measurable effort (other significant contributor)

Supporting Agency: Army Medical Research and Materiel Command

Grants Officer: Snyder, Sandy (sandy.j.snyder.ctr@mail.mil)

Performance Period: 09/15/18 - 09/14/22

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: N.A.

Title: Blood Cell Lipoyxygenase Products -- Formation and Action (R01GM038765-34)

Effort: 3.0 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.

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: Vitamin D and Fish Oil for Autoimmune Disease and Inflammation (R01AR059086-08)

Effort: 0.6 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: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R61HL153011-01)

Effort: 0.24 Calendar Months in Years 2-4 (Co-Investigator) in the R33 Phase of the Award

Supporting Agency: NIH/NHLBI

Grants Officer: Lora Reineck (lora.reineck@nih.gov)

Performance Period: 09/01/22 - 08/31/25 (R33)

Funding Amount: direct costs annually for subcontract

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

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

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

Title: Evaluating Resolution Mechanisms for Infectious Inflammation (R35 GM139430-01)

Effort: 6.6 Calendar Months

Supporting Agency: NIH/NIGMS

Grants Officer: Sarah Dunsmore (dunsmores@nigms.nih.gov)

Performance Period: 04/01/21 - 03/31/26

Funding Amount: annual direct costs

Project Goals: In this R35 MIRA application, the PI shall focus 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.

PENDING:

Title: EPHEDRA: Enhanced PHthisic by Environmental Disruptors of Resolution Agonists

Effort: 2.4 Calendar Months

Supporting Agency: NIH/NIEHS

Grants Officer: Srikanth Nadadur (nadadurs@niehs.nih.gov)

Performance Period: 04/01/22 - 03/31/27

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 the resolution of lung inflammation; 2) Establish the impact of NP disruptors of resolution on viral host responses and post-influenza secondary bacterial pneumonia; and 3) Determine the impact of NP exposure on macrophage efferocytosis, SPM production, pro-resolving receptors and SPM rescue.

Overlap: There is no overlap.

PI PREVIOUS/CURRENT/PENDING SUPPORT

VIDAL MELO, MARCOS

PREVIOUS (last five years)

Project Title: A Prospective, Double-Blind, Randomized, Parallel Design Study to Compare the Hemodynamic and Respiratory Variations during Laparoscopic Surgery in Patients with and without Deep Neuromuscular Blockade

Time Commitment: 0.12 Cal. Mos.

Supporting Agency: Clinical Trial Research Agreement (Vidal Melo); Merck Sharp & Dohme Corp

Funding Agency's Contracting/Grants Officer (name/address): Alfred Saah, MD, MPH;

Merck Sharp & Dohme, 351 North Sumneytown Pike, UG3CD-28, North Wales, PA 19454

Performance Period: 12/13/2013 – 12/12/2016

Funding Amount:

Brief Description of Project's Goals: This study addresses the effects of depth of muscle relaxation during laparoscopic surgery on the process of intraoperative lung derecruitment, central and peripheral gas exchange impairment, and cardiovascular function.

List of Specific Aims: Specific Aim 1: To quantify the dependence of hemodynamic parameters and cardiovascular support on two different depth levels of NMB before, during and after pneumoperitoneum. Specific Aim 2: To determine the impact of two different depth levels of NMB on respiratory mechanics, gas exchange, and oxygen transport to tissues during laparoscopic surgery. Specific Aim 3: To determine the required mean intra-abdominal pressure during laparoscopic surgery with and without deep NMB.

Project Role: PI

Overlap: None

Project Title: Intraoperative Protective Ventilation and Postoperative Pulmonary Complications

Time Commitment: 2.4 Cal. Mos.

Supporting Agency: 5R34-HL123438-03 (Vidal Melo); NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Sunshine Wilson, GM Specialist,
wilsonsa2@mail.nih.gov

Performance Period: 07/15/2015 – 03/31/2019 (NCE)

Funding Amount:

Brief Description of Project's Goals: Our long-term goal is to develop and implement perioperative strategies to eliminate postoperative pulmonary complications.

List of Specific Aims: Specific Aim 1: To characterize usual-care practices for mechanical ventilation during abdominal surgery in major US academic centers. Specific Aim 2: To prospectively compare two methods to individualize PEEP settings in the operating room during abdominal surgery: (1) Maximization of respiratory compliance during a decremental PEEP titration, and (2) Prevention of negative end-expiratory transpulmonary pressures (Ptp). Specific Aim 3: To establish the processes required for the implementation of the full-scale multi-center clinical trial.

Project Role: PI

Overlap: None

Project Title: Regional Tidal Lung Strain and Neutrophilic Inflammation in Early Lung Injury

Time Commitment: 3.12 Cal. Mos.

Supporting Agency: 5R01-HL121228-04 (Vidal Melo); NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Taryn Cobb, GM Specialist; cobbtt@mail.nih.gov

Performance Period: 01/01/2014 – 04/30/2019

Funding Amount:

Brief Description of Project's Goals: We will study how inflammation is produced by regional lung strain during mechanical ventilation, and whether early inflammation is related to subsequent lung damage and dysfunction.

List of Specific Aims: Specific Aim 1: To assess the regional effects of tidal volumetric strain on pulmonary FDG kinetics, tissue neutrophilic inflammation, and neutrophil gene expression. Specific Aim 2: To ascertain the dependence of regional parenchymal damage, neutrophilic inflammation, and lung dysfunction at 24h of lung injury on earlier local cellular metabolic activity quantified with FDG-PET. If FDG uptake during early lung injury measures the initial neutrophilic inflammation triggered by injurious stimuli, then regions of increased uptake should display subsequent effects of that inflammation such as parenchymal damage and dysfunction. Specific Aim 3: Within the first 48h of

mechanical ventilation in septic patients, to establish the relationship between pulmonary neutrophilic inflammation and both regional lung strain and the ensuing degree of lung dysfunction.

Project Role: PI

Overlap: None

Project Title: Preoperative Rehabilitation of Patients Undergoing Flung Resection Surgery

Time Commitment: no measurable effort required

Supporting Agency: MGH-DACCPM

Funding Agency's Contracting/Grants Officer (name/address): Maria Harlow,
Administrative Director, MGH DACCPM Research Council; mharlow@partners.org

Performance Period: 06/01/2016 – 05/31/2018 (NCE)

Funding Amount:

Brief Description of Project's Goals: The goal of this study is to create a comprehensive regimen of preoperative and postoperative interventions that reduce postoperative pulmonary complications and improve high risk patient outcomes.

List of Specific Aims: Specific Aim 1: To establish that a short-term (3 weeks minimum) program of aerobic and strength training in high-risk patients scheduled to undergo curative lung resection can result in a meaningful increase in the 6 minute walk distance (6MWD), a measure associated with functional exercise capacity. Specific Aim 2: To determine if there is a difference in the incidence of postoperative pulmonary complications among those who participate in prehabilitation as compared to controls based on review of clinical outcomes. Specific Aim 3: To assess the changes in inflammatory state associated with a prehabilitation program through immunology assays, RNA sequencing and genetic analysis.

Project Role: PI

Overlap: None

Project Title: 1/2: An Anesthesia-Centered Bundle to Reduce Postoperative Pulmonary Complications: The PRIME-AIR Study

Time Commitment: 0 Cal. Mos.

Supporting Agency: 1UG3-HL140177-01A1 (Vidal Melo); NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Drs. Lora Reineck and James P. Kiley;
lora.reineck@nih.gov, NIH-NHLBI

Performance Period: 12/01/2018 – 02/28/2021 (NCE)

Funding Amount:

Brief Description of Project's 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. If successful, this bundle could change clinical practice and have a substantial impact in reducing postoperative pulmonary morbidity.

List of Specific Aims: Specific Aim 1: To compare the number and severity of PPCs in patients receiving an individualized perioperative anesthesia-centered bundle to those in patients receiving usual anesthetic care during open abdominal surgery. Specific Aim 2: To assess the effect of the proposed bundle on plasma levels of lung injury biomarkers.

Project Role: Contact PI

Overlap: None

CURRENT

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

Time Commitment: 2.04 Cal. Mos.

Supporting Agency: W81XWH1810667 (Choi); Joan & Sanford I. Weill Medical College of Cornell University/ Army Medical Research and Materiel Command

Funding Agency's Contracting/Grants Officer (name/address): Snyder, Sandy; sandy.j.snyder.ctr@mail.mil

Performance Period: 09/15/2018 – 09/14/2022

Funding Amount:

Brief Description of Project's Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS. **List of Specific Aims:** Specific Aim 1: To evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS. Specific Aim 2: To investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome

activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

Project Role: Co-Investigator

Overlap: None

Project Title: PET/CT-guided personalized mechanical ventilation to minimize ventilator induced lung injury

Time Commitment: 2.76 Cal. Mos.

Supporting Agency: 5R01-HL121228-07 (Vidal Melo); NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Lora Reineck, M.D., lora.reineck@nih.gov

Performance Period: 05/01/2019 – 04/30/2024 (*)

Funding Amount:

Brief Description of Project's Goals: We hypothesize that regional lung mechanical deterioration characterized by an increase in strain and aeration heterogeneity with current clinical ventilatory strategies produces changes in pulmonary blood volume conducive to endothelial injury, and composes the substrate for inflammation and early VILI in large heterogeneously inflated lungs. We will test this hypothesis with respiratory-gated PET/CT by using CT-derived lung strains and aeration to ascertain global mechanics measures best indicative of the positive end-expiratory pressure (PEEP) leading to homogenous stretch distributions in sheep.

List of Specific Aims: The specific aims of this project are to use respiratory-gated PET/CT to personalize positive end-expiratory pressure (PEEP) and assess its effect on: (a) strain deterioration, and the spatial relation of this deterioration with tidal capillary closure, endothelial damage, and lung injury in clinically relevant 48h sheep studies; and (b) local distributions of strain and aeration in septic patients.

Project Role: PI (*) project end date at MGH on 10/31/2021

Overlap: None

Project Title: 1/2: An Anesthesia-Centered Bundle to Reduce Postoperative Pulmonary Complications: The PRIME-AIR Study

Time Commitment: 0 Cal. Mos.

Supporting Agency: 4UH3-HL140177-03 (Vidal Melo); NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Drs. Lora Reineck and James P. Kiley; lora.reineck@nih.gov, NIH-NHLBI

Performance Period: 03/19/2019 – 02/28/2022

Funding Amount:

Brief Description of Project's 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. If successful, this bundle could change clinical practice and have a substantial impact in reducing postoperative pulmonary morbidity.

List of Specific Aims: Specific Aim 1: To compare the number and severity of PPCs in patients receiving an individualized perioperative anesthesia-centered bundle to those in patients receiving usual anesthetic care during open abdominal surgery. Specific Aim 2: To assess the effect of the proposed bundle on plasma levels of lung injury biomarkers.

Project Role: Contact PI

Overlap: None

Project Title: 1/2: An Anesthesia-Centered Bundle to Reduce Postoperative Pulmonary Complications: The PRIME-AIR Study

Time Commitment: 2.4 Cal. Mos.

Supporting Agency: 5UH3-HL140177-03 (Vidal Melo); NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Drs. Lora Reineck and James P. Kiley; lora.reineck@nih.gov, NIH-NHLBI

Performance Period: 12/01/2018 – 10/31/2021 (*)

Funding Amount:

Brief Description of Project's 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. If successful, this bundle could change clinical practice and have a substantial impact in reducing postoperative pulmonary morbidity.

List of Specific Aims: Specific Aim 1: To compare the number and severity of PPCs in patients receiving an individualized perioperative anesthesia-centered bundle to those in patients receiving usual anesthetic care during open abdominal surgery. Specific Aim 2: To assess the effect of the proposed bundle on plasma levels of lung injury biomarkers.

Project Role: Contact PI (*) project end date at MGH on 10/31/2021

Overlap: None

Project Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS **Goals:** The overall goal is to investigate a personalized medicine approach to inhaled CO (iCO) treatment in patients with sepsis-induced ARDS.

Time Commitment: 2.4 Cal. Mos.

Supporting Agency: R61-HL153011-01 (Choi, Fredenburgh); Joan & Sanford I. Weill Medical College of Cornell University/NIH-NHLBI

Funding Agency's Contracting/Grants Officer (name/address): Reineck, Lora A. (lora.reineck@nih.gov), National Heart, Lung and Blood Institute, Two Rockledge Center, Suite 10042 6701 Rockledge Dr. MSC 7952 Bethesda, Maryland 20892-7952

Performance Period: 09/01/2020 – 08/31/2025 (*)

Funding Amount:

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-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 PI (*) anticipates starting project in Year 2 in R33 Phase on 09/01/2021, pending subcontract agreement execution

Overlap: None

PENDING

Project Title: TRICS IV - Restrictive versus Liberal Transfusion in Younger Patients Undergoing Cardiac Surgery

Time Commitment: 0.24 Cal. Mos.

Supporting Agency: The Cooper Health System A New Jersey Non-Profit Corporation/NIH

Funding Agency's Contracting/Grants Officer (name/address): N/A

Performance Period: 12/01/2021 - 11/30/2024

Funding Amount:

Description of Project Goals: This clinical trial represents an important step towards determining the optimal transfusion trigger for moderate to high risk patients =< 65 years of age undergoing cardiac surgery.

Specific Aims: N/A

Role: Site PI

Overlap: None

Project Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R33)

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

Time Commitment: 2.4 CM

Supporting Agency: NIH/NHLBI

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

Performance Period: R33 09/01/2022 – 08/31/2025

Funding Amount:

Goals/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 PI

Overlap: The pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a

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

* This study has been funded, grant R61 HL153011, project dates 09/15/2020 – 08/31/2021, however MGH is not participating in the R61 Phase and will join the project in year 2 in the R33 Phase starting 09/01/2022.

KEY PERSONNEL CURRENT/ PREVIOUS/ PENDING SUPPORT

THOMPSON, B. TAYLOR

CURRENT

Title: CCC for NHLBI Prevention and Early Treatment of Acute Lung Injury PETAL Network

Time Commitments: 40% (4.80 CM)

Supporting Agency: NHLBI- National Heart, Lung and Blood Institute,

Grants Officer: Lora Reineck M.D., M.S | lora.reineck@nih.gov | 5U01HL123009-07S1&2

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.

Overlap: None

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 Materiel Command

Contracting/Grants Officer: Snyder, Sandy | sandy.j.snyder.ctr@mail.mil | W81XWH1810667

Performance Period: 09/15/2018-09/14/2022

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).

Overlap: None

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

Performance Period: 01/16/2018-12/31/2024

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.

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

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

Overlap: None

Title: 1/2: An Anesthesia-Centered Bundle to Reduce Postoperative Pulmonary Complications: The PRIME-AIR Study

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 | 5UH3HL140177-03

Performance Period: 03/19/2019-10/31/2021

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.

Overlap: None

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

Time Commitments: 25% (3.00 CM)

Supporting Agency: NHLBI via Research Triangle Institute

Grants Officer: Antonello Punturieri, M.D., Ph.D. | punturiera@nhlbi.nih.gov | 1OT2HL156812

Performance Period: 06/01/2020-05/31/2022

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 17,791,854 United States through the International Coordinating Center at the Massachusetts General Hospital.

Overlap: None

Title: Biomarkers of Interstitial Lung Abnormalities 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

Performance Period: 09/01/2019-08/31/2022

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.

Overlap: None

PREVIOUS

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

Title: PETAL COVID-19 Observational Study (CORAL) **Goals:** The purpose is deep phenotyping of COVID-19 patients. **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: **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

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

Title: Core B-Clinical Studies Coordinator Care Carbon Monoxide: Novel Opportunities for Therapy **Supporting Agency:** BWH/NIH/NHLBI

Grants Officer: Andrea Harabin | andrea.harabin@nih.gov | 5P01HL108801-05

Performance Period: 08/15/2011-06/30/2016

Level of funding: **Project Goals:** This study seeks to test the hypothesis that carbon monoxide can provide tissue protective effects in sepsis and acute lung injury by preserving cellular homeostasis and promoting bacterial clearance.

Specific Aims: Aim 1: To identify patients with the systemic inflammatory response syndrome (SIRS), sepsis, and sepsis-induced acute lung injury (ALI); to collect and store plasma, RNA, and primary cells from subjects in a clinical biorepository; and to provide biostatistical support for Projects 1-4 for the analysis and interpretation of studies performed using these specimens.

Aim 2: To serve as the DCC for the Phase 1 first-in-ALI safety study for inhaled CO in sepsis induced ALI in Project 1 and proof-of-concept study with collection of muscle biopsies after inhaled CO in Project

Role: Core B PI

PENDING

Project Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R33)

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

Time Commitment: 2.4 CM

Supporting Agency: NIH/NHLBI

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

Performance Period: R33 09/01/2022 – 08/31/2025

Funding Amount:

Goals/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 PI

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

* This study has been funded, grant R61 HL153011, project dates 09/15/2020 – 08/31/2021, however MGH is not participating in the R61 Phase and will join the project in year 2 in the R33 Phase starting 09/01/2022.

KEY PERSONNEL PREVIOUS/CURRENT/PENDING SUPPORT

SAILLANT, NOELLE

PREVIOUS

Award Number: R01HL119248 (De, Survraru)

Award Period: 04/01/2014-03/31/2018

Funding Source: NIH/NHLBI/Rensselaer Polytechnic Institute

Award Amount: (total direct costs awarded)

Title: *Development and Validation of a Virtual Skill Trainer (VAST)* Program Official: Punturieri, Antonello, punturieri@nhlbi.nih.gov

Goal: To develop a virtual reality cricothyroidotomy trainer for medical education.

Specific Aims: (SA1) Design and develop the Virtual Airway Skill Trainer (VAST) platform. Specifically, we will develop (1) physics-based computational models of human anatomy based upon in vivo experimental studies; (2) an immersive 3D high definition (HD) head mounted display (HMD) system to represent the clinical environment (OR/ICU/ED); and (3) an innovative bi-manual force feedback hardware interface with tactile matrix gloves that allows representation of various patient anatomies associated with the difficult airway. (SA 2) Develop simulation scenarios for endotracheal intubation (ETI) and cricothyrotomy (CCT) procedures within the VAST by integrating the computational models and experimental data generated in SA1.

Effort: 0.06 cm

Role: Co-Investigator (PI, MGH subcontract)

CURRENT

Award Number: W81XWH1810667 (Choi, Augustine)

Award Period: 09/15/2018-09/14/2022

Funding Source: Army Medical Research and Material Command

Award Amount:

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

Grants Officer: Snyder, Sandy, sandy.j.snyder.ctr@mail.mil

Goals: The major goal of this study is to evaluate safety, tolerability, and efficacy of inhaled CO at a fixed dose of 200 ppm in patients with ARDS.

Specific Aims: The specific aims of this project are 1) to evaluate safety, tolerability, and efficacy of low dose inhaled CO (iCO) at a fixed dose of 200 ppm in patients with ARDS; and 2) to investigate the effects of iCO on biomarkers of mitochondrial dysfunction and inflammasome activation in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

Effort: 0.24 CM

Role: Co-Investigator

Award Number: 7000442543

Award Period: 10/01/2018 - 09/30/2021

Title: Medic-AIDE (AI for Decision Emulation)

Funding Source: Massachusetts Institute of technology

Funding Amount: (MGH)

Grants Officer: Sara Eagan, sara.eagan@ll.mit.edu ,

Goals: The major goal of this study is to develop Artificial Intelligence (AI) to help with triage predictions in Trauma Patients

Specific Aims: The specific aims of this project are 1) to develop and train an AI model for prehospital triage 2) To use AI to predict massive transfusion, shock and need for surgery 3.) To use AI to anatomic injuries from external wounds and vital signs

Effort: 0.6 CM

Role: Co-Investigator (PI, MGH subcontract)

PENDING

None

OVERLAP

None

ACTIVE/PENDING/PREVIOUS SUPPORT

KAREN WELTY-WOLF

Dr. Welty-Wolf holds dual appointments at Duke University and the Durham VAMC (7/8) constituting her total professional effort (TPE). The following list includes Dr. Welty-Wolf's effort commitments and all financial resources available in support of her research activities. Calendar months were calculated using only Duke University effort, not total professional effort.

DUKE ACTIVE

Title: Mitochondrial Quality Control and Alveolar Damage Resolution After Acute Lung Injury

Effort: 25% / 3.0 calendar months

Supporting Agency: NIH/NHLBI R01-HL135239-04

Grants Officer: Louis Velasco, louis.velasco@nih.gov; 301-827-7977

Performance Period: 08/10/2017-06/30/2022

Funding Amount: Total Costs

Goals: This project aims to define 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

VA ACTIVE

Title: Mechanisms of Alveolar Mitochondrial Damage and Resolution in Pneumonia

Time Commitment: 25% / 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

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R33)

Effort: 25% / 3.0 calendar months (Site PI)

Supporting Agency: Weill Cornell Medicine/NIH/NHLBI

Contracting/Grants Officer: TBD, Office of Sponsored Research Admin, subawards-wcmc@med.cornell.edu; 646-962-8290 / NIH Lora Reineck (lora.reineck@nih.gov)

Performance Period: 09/01/2021* – 08/31/2025

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

** This study has been funded, grant R61 HL153011, project dates 09/15/2020 – 08/31/2022, however Duke is not participating in the R61 Phase and will join the project in year 2 in the R33 Phase. A start date for the R33 Phase is anticipated to begin 09/01/2022.*

VA PENDING

None

PREVIOUS (last 5 years)

Title: Novel Dialysis-Like Therapeutics in Sepsis-induced Shock and Organ Failure (Welty-Wolf)

Effort: 20% / 2.40 calendar months

Supporting Agency: Defense Advanced Research Projects Agency HR0011-15-2-0057

Grants Officer: 675 North Randolph St. Arlington, VA. 22203-2114

Performance Period: 9/28/2015 – 05/31/2018

Funding Amount:

Goals: The main goals of this project are to determine the efficacy and safety of hemadsorption therapy during pneumococcal sepsis using a novel DLT device, measuring effect on clearance of bacteria and cytokines from the blood.

Specific Aims: 1. Determine the efficacy of hemadsorption therapy using a novel DLT device.

2. Determine the safety of DLT hemadsorption in baboons with pneumococcal pneumonia and sepsis.

Overlap: None

Title: Project 2: Regulation of Mitochondrial Quality Control by HO-1 System in Sepsis (Piantadosi)

Effort: 78% / 9.48 calendar months

Supporting Agency: Brigham and Women's Hospital 107287

Grants Officer: Paul J Anderson, 75 Francis St. Boston MA 02115

Performance Period: 08/15/2011 – 06/30/2017

Funding Amount:

Goals: The overall goal is to demonstrate that HO/CO-induced transcriptional activation of mitochondrial biogenesis in sepsis generates an anti-inflammatory response through NFE2L2 and NRF-1 that is implemented by IL-10 and/or SOCS3 up-regulation, and which suppresses pro-inflammatory cytokine production and activates mitophagy.

Specific Aims: The specific aims of this project are to: i) elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection, ii) identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI, and iii) provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI at the next Cycle II of the translational PPG program.

Overlap: None

PREVIOUS/CURRENT/PENDING SUPPORT:

VATSAAS, CORY

CURRENT:

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

Effort: 2% /0.24 calendar months (Co-Investigator)

Supporting Agency: Department of Defense 181691-02/W81XWH1810667

Name and address of Contracting/Grants Officer: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil

Funding: Direct Costs, Total Costs

Performance Period: 09/15/2018 – 09/14/2022

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: **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

PENDING:

None

PREVIOUS:

None

OTHER SUPPORT

KRAFT, Bryan

Dr. Kraft held a dual appointment at Duke University and the Durham VAMC (1/8), constituting his total profession effort (TPE). Calendar months were calculated using only Duke University effort, not total professional effort, and reflect his last reported effort at Duke University. Dr. Kraft terminated with Duke University on September 19, 2021.

DUKE ACTIVE

Title: Role of S-nitrosothiols in Akt1 signaling and pneumonia resolution

Role: PI

Supporting Agency: National Institutes of Health – NHLBI (5K08-HL130557-04)

Time Commitment: 89% / 10.68 CM

Address: National Heart, Lung and Blood Institute Building 31, 31 Center Drive, Bethesda, MD 20892

Contracting/Grants Officer: Loius Velasco, louis.velasco@nih.gov; 301-827-7977

Performance Period: 1/15/2017-9/19/2021

Level of Funding:

Project 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.

Specific 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.

Overlap: There is no scientific, budgetary or effort overlap for Dr. Kraft

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

Role: Co-Investigator

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

Time Commitment: 5% / 0.6 CM

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

Contracting/Grants Officer: Aleta Gunsul, Director, Office of Sponsored Research Admin, subawards-wcmc@med.cornell.edu; 646-962-8290

Performance Period: 9/15/2018-9/14/2020

Level of Funding:

Project 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).

Specific 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.

Overlap: There is no scientific, budgetary or effort overlap for Dr. Kraft

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)

Role: Site PI

Supporting Agency: The Marcus Foundation

Time Commitment: 1% / 0.12 CM

Address: The Marcus Foundation 1266 West Paces Ferry Road, Ste. 615, Atlanta, GA 30327-2306

Contracting/Grants Officer: Ryan Braid, rbraid@marcusfoundation.org

Performance Period: 5/1/2020-11/30/2022

Level of Funding: per patient (anticipated enrollment of 1-2 patients)

Project Goals/Specific Aims: 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.

Overlap: There is no scientific, budgetary or effort overlap for Dr. Kraft

VAMC ACTIVE

None

DUKE PENDING

Title: ICU COVID-10 Biorepository Plasma Samples

Role: PI

Supporting Agency: Grifols Worldwide Operations

Time Commitment: 1% / 0.12 CM

Contracting/Grants Officer: To be Assigned

Performance Period: 03/09/2021*-09/09/2022

Level of Funding: (Total Costs)

Project Goals/Aims: This study is a transfer of Duke owned plasma samples collected as part of the Duke ICU COVID-19 Biorepository to Grifols to run proteomic analysis. The data will be returned to Duke researchers for analysis.

Overlap: This study will make use of ICU Biorepository samples, however there is no scientific, budgetary or effort overlap for Dr. Kraft.

**Award notification is forthcoming from sponsor*

Title: Remotely Monitored, Mobile Health-Supported High Intensity Interval Training After COVID-19 Critical Illness (REMM HIIT-COVID-19)

Role: Co-Investigator

Supporting Agency: NIH / R01-HD107103-01

Time Commitment: 5% / 0.6 CM

Contracting/Grants Officer: To be Assigned

Performance Period: 9/1/2021-8/31/2026

Level of Funding: (Direct Costs)

Project Goals/Aims: REMM-HIIT-COVID-19 study [REmotely Monitored, Mobile health-supported High Intensity Interval Training after COVID-19 Critical Illness] to test the hypothesis that the REMM-HIIT-COVID-19 exercise intervention, in contrast to exercise education alone, will (Aim 1) improve cardiorespiratory fitness as well as muscle strength and muscle mass, (Aim 2), improve physical function as assessed by six-minute walk distance at 3 months after hospital discharge and other quality of life, functional, mental health and cognitive outcomes (Aim 3) improve markers of mitochondrial function and biomarkers of inflammation and aging in addition to measures of cognition and mental health outcomes.

Overlap: There is no scientific, budgetary or effort overlap for Dr. Kraft.

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

Role: Co-Investigator

Supporting Agency: Weill Medical College of Cornell University / NIH

Time Commitment: 20% / 2.4 CM

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

Contracting/Grants Officer: TBD, Office of Sponsored Research Admin, subawards-wcmc@med.cornell.edu; 646-962-8290

Performance Period: 07/01/2021*-06/30/2024

Level of Funding: (total costs)

Project Goals/Specific Aims: The goal of this translational P01 is to advance the field of carbon monoxide (CO) therapeutics in a Phase Ib/IIa interventional trial of inhaled CO in subjects with sepsis-induced acute respiratory distress syndrome (ARDS). Duke University Hospital is one of four clinical enrollment sites for the proposed study and as such has a target enrollment of 5 subjects per year for each of the first four years of the P01. Study activities will be coordinated through the Data Coordinating Center (DCC) in Boston, where randomization assignments will be made to inhaled CO or placebo. Study data will be entered into a RedCap database administered by Core B of the P01. Research blood samples will be collected pre- and post-CO administration according to the IRB approved protocol and will be managed through the study's specimen biorepository at Brigham and Women's Hospital (Core B) for support of investigations in Projects 1-3 of the P01.

Overlap: There is no scientific, budgetary or effort overlap for Dr. Kraft

**Study start date has been delayed; new effective date not yet determined*

Title: Tfam Protects Mitochondrial Integrity and Quality in Acute Lung Injury

Role: Co-Investigator

Supporting Agency: NIH

Time Commitment: 15% / 1.8 CM

Contracting/Grants Officer: To be Assigned

Performance Period: 9/1/2021-8/31/2025

Level of Funding: (Direct Costs)

Project Goals: The overall objective is to (i) identify the molecular mechanisms by which Tfam regulates mitochondrial integrity and function, oxidative stress and inflammasome formation in AT2 cells, and (ii) determine the importance of Tfam gene expression in immune response activation and recovery from infection. Using a validated *S. aureus*/pneumonia model in mice and complementary human lung cell and tissue studies, we will seek proof-of-principle for an integrated genetic network that improves mitochondrial and cell survival and reduces lung inflammation in ALI. The discovery of such a network would support our hypothesis that Tfam loss of function leads to enhanced mitochondrial DNA release and further propagating tissue injury. We propose that Tfam regulates mitochondrial integrity and quality in lung alveolar epithelial cells and facilitate protection in ALI/pneumonia by enhancing mitochondrial biogenesis, energy production, mitophagy, block mtDNA release, enhance natural immune responses, and control inflammation. Depletion of Tfam in alveolar epithelial cells exacerbates inflammation and ARDS severity. The network would also restore the respiration needed for alveolar epithelial repair, e.g. through AT2 cell proliferation, differentiation and AT1 cell replacement. The translational studies in human lung cells and tissue will help validate these concepts in ARDS, and help unlock mitochondrial therapies for ALI/ARDS resolution.

Specific Aims: **Aim 1:** Measure mitochondrial quality, integrity and oxidative damage in AT2 cells from Tfam knockout and wild type littermate mice infected with *S. aureus* ALI/pneumonia. Based on preliminary data, our working hypothesis is that Tfam gene and protein expression is crucial for mitochondrial integrity, quality, and function and AEC cellular homeostasis. **Aim 2:** Define the molecular mechanisms responsible for suppression of Tfam function that impacts alveolar mitochondrial integrity and morphology in mice infected with live *S. aureus*; and determine the contribution of Tfam to mtDNA protection and prevention from release into the lung. Based on preliminary data, our working hypothesis is that Tfam loss-of-function will promote mitochondrial dysfunction, mtDNA release, inflammation, and organ damage. **Aim 3:** Translate the molecular mechanisms in mice to patients with and without ARDS by measuring Tfam mRNA and protein expression, free mtDNA, and immune cells to sites of alveolar cell death and necrotic foci in human fixed lung tissue. Based on preliminary data, our working hypothesis is that damaged mitochondria and freely existent mtDNA would correlate with the severity of pathology and survival.

Overlap: There is no scientific, budgetary or effort overlap for Dr. Kraft.

VAMC PENDING

None

DUKE PAST SUPPORT

Title: IMPALA MOL-PAP-002 A randomized double blind placebo controlled multicentre clinical trial of inhaled molgramostim in autoimmune pulmonary alveolar proteinosis patients

Role: PI

Supporting Agency: Savara Inc.

Time Commitment: 2% / 0.24 CM

Address: Savara Inc. 6836 Bee Caves Rd., Bldg III, Ste 200, Austin, TX

Contracting/Grants Officer: Jessica Jackson, Director of Clinical Operations, Jessica.jackson@savarapharma.com; 855-298-2020

Performance Period: 8/20/2018-12/19/2019

Level of Funding:

Project 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.

Specific 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.

Title: Project 2: Carbon Monoxide: Novel Opportunities for Therapy

Role: Investigator

Supporting Agency: The Brigham & Women's Hospital (Sub Agreement #102787)/NIH (P01-HL108801-05)

Time Commitment: 25% / 3.0 CM

Address: Brigham & Women's Hospital 101 Huntington Avenue, Boston, MA 02199

Contracting/Grants Officer: Lisa Griffin, Director Sponsored Programs, lgriffin11@bwh.harvard.edu; 617-525-8833

Performance Period: 8/15/2011-6/30/2017

Level of Funding:

Project Goals/Specific Aims: The overall goal is to demonstrate that HO/CO-induced transcriptional activation of mitochondrial biogenesis in sepsis generates an anti-inflammatory response through NFE2I2 and NRF-1 that is implemented by IL-10 and/or SOCS3 up-regulation, and which suppresses pro-inflammatory cytokine production and activates mitophagy.

Specific Aims: The specific aims of this project are to: i) elucidate novel physiologic and cellular mechanism(s) by which a toxic molecule when administered at low physiologic doses can provide potent cytoprotection, ii) identify novel molecular targets of CO which can by themselves be a platform for the development of both diagnostic and therapeutic modalities in ALI, and iii) provide critical proof-of-concept "first in ALI" studies to prepare us for a CO intervention trial in ALI at the next Cycle II of the translational PPG program.

Title: Novel Dialysis-Like Therapeutics in Sepsis-Induced Shock and Organ Failure

Role: Co-Investigator

Supporting Agency: Defense Advanced Research Projects Agency (HR0011-15-2-0057)

Time Commitment: 30% / 3.6 CM

Address: DARPA 675 N. Randolph Street, Arlington, VA 22203-2114

Contracting/Grants Officer: Susan Shean, susan.shean@darpa.mil; 703-526-4128

Performance Period: 9/28/2015-5/31/2018

Level of Funding:

Project 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.

Specific Aims: 1) Perform dose-ranging studies to develop model for *S. pneumoniae* 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.

VA PAST SUPPORT

None

ACTIVE/PENDING/PREVIOUS SUPPORT:

DAVIES, JOHN

ACTIVE

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

Effort: 40% / 4.8 calendar months

Supporting Agency: Weill Medical College of Cornell University /Department of Defense 181691-02/W81XWH1810667

Contact Name and Address: Lisa M. Sawyer Phone: 301-619-6661 Email: lisa.m.sawyer22.civ@mail.mil

Performance Period: 09/15/2018 – 09/14/2022

Level of Funding: Direct Costs, Total Costs

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: Prospective trial to validate safety of Hemolung Respiratory Assist System for COPD patients (Rackley)

Effort: 10% / 1.2 calendar months

Supporting Agency: Alung Technologies

Contact Name and Address: Marci Halevi, Senior Director, Clinical Trial Operations, ALUNG Technologies, Inc., 2500 Jane Street, Suite 1, Pittsburgh, PA, Phone #: 917-912-2510; Email: mhalevi@alung.com

Performance Period: 05/16/2018 – 05/31/2023

Level of Funding: Direct Costs, Total Costs

Goals: To demonstrate the safety and efficacy of using the Hemolung RAS to provide low-flow ECCO2R as an alternative or adjunct to invasive mechanical ventilation versus standard of care invasive mechanical ventilation alone to increase ventilator-free days for COPD patients who require respiratory support due to an acute exacerbation of their COPD.

Specific Aims: To validate the safety and efficacy of the Hemolung Respiratory Assist System (RAS) for COPD patients experiencing acute exacerbations requiring ventilatory support.

Overlap: None

PENDING

Title: A Phase Ib Study of Inhaled CO for the Treatment of Sepsis-Induced ARDS (R33)

Effort: 33.33% / 4.0 calendar months Clinical Research Coordinator

Supporting Agency: Weill Cornell Medicine/ NIH/NHLBI

Contracting/Grants Officer: TBD, Office of Sponsored Research Admin, subawards-wcmc@med.cornell.edu; 646-962-8290 / NIH Lora Reineck (lora.reineck@nih.gov)

Performance Period: 09/01/2021* – 08/31/2024

Funding Amount: Direct Costs, Total 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 pending Phase Ib study is distinct and has no scientific or budgetary overlap with the current Phase II trial supported by the Department of Defense. The pending Phase Ib study proposes to examine the safety and accuracy of a CFK equation-based personalized dosing algorithm to achieve a carboxyhemoglobin level of 6-8% in patients with sepsis-induced ARDS. The ongoing Phase II trial is evaluating the safety and efficacy of a fixed dose of inhaled CO at 200 ppm

on lung injury score and other clinical outcomes in patients with ARDS, with a focus on ARDS secondary to trauma, transfusion, burns, hemorrhagic shock, inhalation, and/or oxygen exposure (FY17 PRMRP Area of Encouragement).

** This study has been funded, grant R61 HL153011, project dates 09/15/2020 – 08/31/2021, however Duke is not participating in the R61 Phase and will join the project in year 2 in the R33 Phase. Effective date of R33 Phase has been delayed; new effective date TBD.*

PREVIOUS (Past 5 years)

None

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: Jeremy 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 2022

Study Goals:

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

Specific Aims:

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

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

Key Accomplishments and Outcomes:

Publications: None to date

Patents: None to date

Funding Obtained: None to date