AWARD NUMBER: W81XWH-17-1-0631

TITLE: Mesenchymal Stem cells for Treatment of ARDS Following Trauma

PRINCIPAL INVESTIGATOR: Michael A. Matthay, M.D.

CONTRACTING ORGANIZATION: Regents of the University of California, San Francisco
San Francisco, CA 94103

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6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Regents of the University of California, San Francisco
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San Francisco, CA 94143

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14. ABSTRACT

The acute respiratory distress syndrome (ARDS) is a life-threatening medical condition in which the lung is injured or inflamed to the degree that it cannot properly exchange gases and oxygenate the body. ARDS can be caused by a variety of conditions including trauma, severe blood loss, multiple or large volume blood transfusions, burns, and infections. The development of therapeutics that can limit the severity and/or progression of lung injuries that lead to ARDS and death is an immediate clinical need in both military and civilian sectors. Experimental studies carried out in small and large animals have demonstrated that specialized cells called mesenchymal stromal cells (MSC) can effectively reduce inflammation in multiple diseases including ARDS. The overall objective of this proposal is to carry out a randomized, blinded, placebo-controlled, multicenter phase 2b trial to test the therapeutic potential of allogeneic bone-marrow derived MSC for treating ARDS, with a major focus on civilian trauma patients. The specific aims of this project are: **Specific Aim 1**. To test the clinical efficacy of intravenously delivered allogeneic human MSC in patients with ARDS. **Specific Aim 2.** To test the mechanisms by which MSC reduce acute lung injury in trauma patients with ARDS.

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1. **INTRODUCTION:**

The acute respiratory distress syndrome (ARDS) is a life-threatening medical condition in which the lung is injured or inflamed to the degree that it cannot properly exchange gases and oxygenate the body. ARDS can be caused by a variety of conditions including infections, trauma, severe blood loss, multiple or large volume blood transfusions, burns, and the inhalation of chemical poisons or smoke. According to the National Heart Lung and Blood Institute, approximately 190,000 people in the U.S. will develop ARDS each year, with a death rate ranging from 25–40%. Recent studies from the Department of Defense Iraq Trauma Registry (DoDTR) reported that ARDS developed in a large number of severely wounded warfighters and was associated with higher death rates. To date, there have been few advances in the treatment of major trauma related conditions such as ARDS. The development of therapeutics that can limit the severity and/or progression of lung injuries that lead to ARDS and death is an immediate clinical need in both military and civilian sectors. Experimental studies carried out in small and large animals have demonstrated that specialized cells called mesenchymal stromal cells (MSC) can effectively reduce inflammation in multiple diseases including ARDS. The overall objective of this proposal is to carry out a randomized, blinded, placebo-controlled, multicenter phase 2b trial to test the therapeutic potential of allogeneic bone-marrow derived MSC for treating ARDS, with a major focus on civilian trauma patients. The specific aims of this project are: **Specific Aim 1**. To test the clinical efficacy of intravenously delivered allogeneic human MSC in patients with ARDS. **Specific Aim 2.** To test the mechanisms by which MSC reduce acute lung injury in trauma patients with ARDS.

2. **KEYWORDS:** Acute respiratory distress syndrome, pulmonary edema, trauma, pneumonia, sepsis

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

  During Year 1, we had 4 major goals as follows:

  1. Execute contracts with other sites
  2. Prepare research protocol for FDA modification of IND and IRB submissions and HRPO approval
     a. Prepare Regulatory Documents and Research Protocol
     b. Prepare FDA submission
     c. Prepare IRB submissions
     d. Milestones for this task: submission to FDA of modified IND, IRB approval at all sites, HRPO approval, secondary Army approval
     e. Establish a DSMB for this trial
  3. Coordinate study staff for clinical trials
     a. Milestones for this task: research staff trained
  4. Finalize data management system and eCRFs
     a. Milestone for this task: Data management system completed

- **What was accomplished under these goals?**

  Major Activities, **Objectives, Results and Significant Results**

  1. Contracts (subawards) have been executed at all the participating sites (Vanderbilt University Medical Center; Harborview Medical Center - U. Washington, Oregon Health Science Center; University of Texas Medical Center, Houston).

2. Prepare research protocol for FDA modification of IND and IRB submissions and HRPO approval

a. Initial protocol approved by FDA with IND (January 2018). Further modifications in the protocol are needed: specifically, the prior bone marrow source has stopped supplying healthy marrows. Therefore, we have been working to qualify a new bone marrow source for the production of the allogeneic human mesenchymal stromal cells at the University of Minnesota NIH/NHLBI production center. We anticipate revision of the manufacturing section of the protocol to be completed in October 2018. Modifications to the inclusion criteria to include patients with trauma and non-traumatic causes of ARDS have been developed, reviewed with the DoD Science Officer, Sandy Snyder, and will be submitted along with the modifications described above.

b. Prepare FDA submission – Completed in Jan 2018, but with a planned modification to be submitted in November 2018.

c. Prepare IRB submissions – Since the original grant submission, this goal was revised to use a central IRB rather than the IRBs at each local site in order to maximize efficiency and standardize reporting. During the first year, we have worked with each performance site (University of California Zuckerberg San Francisco General Hospital and UCSF Medical Center, Oregon Health Science Center, Harborview Medical Center, Seattle, WA, the University of Texas Medical Center, Houston, Texas and Vanderbilt University Medical Center, Nashville, TN) to execute reliance agreements to allow the Vanderbilt IRB to function as the central IRB. The central IRB has reviewed and approved our protocol and consent forms; we will submit a modification to reflect changes to the manufacturing protocol and inclusion criteria in November 2018.

d. Milestones – Submission of modified IND, IRB approval at all sites, HRPO approval and secondary Army approval – these are pending

e. DSMB – We have established a DSMB for this trial; membership has been reviewed and approved by the DoD.

3. Coordinate study staff for clinical trials.

a. Train research staff – We had a videoconference meeting with approximately 50 participants from all sites for 3 hours on August 30, 2018. Participants included our Scientific Officer, Sandy Snyder, investigators, coordinators, and the bone marrow and cell therapy laboratory personnel. We plan to further advance this training with monthly calls on the second Thursday in the month beginning in November 2018. We are also creating a laboratory manual of standard operating procedures for each of the participating clinical site cell and bone marrow facilities for processing of the cryopreserved MSCs (or placebo) for administration at each of the clinical sites.

4. Finalize data management system and eCRFS. The HIPPA compliant data management system has been created. We are now beta-testing the data management system, especially focusing on data entry, real-time data validation and data export functions. Minor database modifications will be needed for the pending revised protocol.

We have also set up a plan regarding the tracking system using barcodes to track and store biological samples.

Discussion of stated goals that have not been met. The need to find and qualify a new source of bone marrow for the production of MSCs and to revise our protocol to reflect this change in product manufacturing delayed our timeline. We have identified and qualified this new source (AssureImmune [Miami, FL). At the same time, Dr. McKenna (PI at the University of Minnesota) has worked with his group to modify the production process slightly to maximize cell viability. Dr. McKenna is modifying the CMC section of the Clinical Protocol at present to reflect these changes. We have also been slightly delayed by broadening the inclusion criteria to include both traumatic and non-traumatic causes of ARDS, although this modification has been positive and will help make the value of this trial greater and more generalizable in both the military and civilian population.

- **What opportunities for training and professional development has the project provided?** Nothing to report.

- **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? –** We will complete the submission of the revised protocol to FDA, the central IRB and to the DoD (HRPO) for final approval. We will also complete the eCRFs, electronic consent forms (already approved by Vanderbilt IRB), specimen tracking system and all the training to investigators, coordinators, and bone marrow and cell therapy personnel to be able to initiate the trial.

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:**
   The Principal Site Investigator at Vanderbilt Medical Center (Addison May, MD) moved on to another university and therefore we appointed a new Principal Site Investigator, Lorraine B. Ware, MD Professor of Medicine who was the previous Co-site Investigator at Vanderbilt. Dr. Ware is experienced in clinical trials and has worked with Dr. Matthay for several years on many projects. We are also adding investigators in the medical intensive care units at each clinical site.

   We have modified the source of bone marrow and study inclusion criteria as described in detail above. All of the changes described in this Annual Report have been discussed in detail with our Science Officer, Sandy Snyder and Kevin R. Moore, Grants Officer.

   - **Changes in approach and reasons for change –** Our Science Officer Sandy Snyder has reviewed and approved the broadened inclusion criteria to both traumatic and non-traumatic causes of ARDS.

   Actual or anticipated problems or delays and actions or plans to resolve them
   - As explained above, the primary reason for the delay in beginning the trial was the need to find a new source of human bone marrow since the prior vendor (Lonza) unexpectedly announced in May 2018 that they would no longer supply human bone marrow to private or public entities.

- **Changes that had a significant impact on expenditures –** expenditures during this first year have been minimal at each of the four subaward sites since the clinical trial has not started.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents –** The initial IRB approval for this study was issued by Vanderbilt University as our central IRB on April 30, 2018. We plan minor protocol modifications to broaden inclusion criteria and to reflect changes in product manufacturing; these have been reviewed by our DoD Science Officer. These changes will be formally reviewed by the FDA, DoD and central IRB prior to study initiation

  There is nothing to report for vertebrate animals, biohazards, or select agents.

6. **PRODUCTS:**
   - **Publications, conference papers, and presentations:** Nothing to report.
   - **Website(s) or other Internet site(s)**: Nothing to report.
   - **Technologies or techniques:** Nothing to report.

   - **Inventions, patent applications, and/or licenses:** Nothing to report.
   - **Other Products**: Nothing to report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:**
   - **What individuals have worked on the project?**

     Michael A. Matthay MD
     Project Role: Principal Investigator
     Research Identifier:0000-0001-2345-6789
     Nearest person month worked: 4.40
     Contribution to Project: Revised the FDA approved Clinical Protocol and Investigator Brochure for submission to the Vanderbilt cIRB; communicated with all of the sites (4 sites in addition to UCSF) by conference calls and by emails and phone calls; supervised the preparation of the case report form and submitted to our data management firm (Quesgen); working on the plans for a central IRB at Vanderbilt with Hanjing Zhuo and Kathleen Liu; worked with UCSF Research Management Services (Sara Yturralde) on the budget for UCSF and the other sites; communicated with FDA by email; communicated with the Dave McKenna, MD at the University of Minnesota regarding details for production of the mesenchymal stromal cells for the trial and has nearly completed this contract; organized mock screening for the trial; worked on the randomization scheme; communicated with DoD and Brian Garland.

     Kathleen D. Liu, MD, PhD, MAS
     Project Role: Co-Investigator
     Research Identifier: 0000-0001-2345-6789
     Nearest person month worked: 0.55
     Contribution to Project: Worked with Dr. Matthay to write and edit the Clinical Protocol; advised Dr. Matthay on the plans for a central IRB at Vanderbilt and spoke directly with the Head of that cIRB, Dr. Todd Rice; helped plan completion of Statement of Work Tasks and the case report form; helped to oversee Hanjing Zhou, the project manager.

     Carolyn Calfee, MD MAS
     Project Role: Co-Investigator

Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 0.45
Contribution to Project: Worked with Dr. Matthay on editing the clinical protocol, the screening form, and Case Report Form.

Carolyn Hendrickson, MD, MAS
Project Role: Co-Investigator
Research Identifier: 0000-0001-2345-6789
Nearest person month worked:1.10
Contribution to Project: Worked with Dr. Matthay to prepare the Clinical Protocol and the case report form and the screening form and to initiate mock screening.

Rachael Calcutt, MD, MAS
Project Role: Co-Investigator
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 0.50
Contribution to Project: Worked with Dr. Matthay to write and edit the Clinical Protocol and to edit the case report form for the cIRB and for mock screening.

Hanjing Zhuo, BS, MPH
Project Role: Project Manager
Research Identifier 0000-0001-2345-6789:
Nearest person month worked: 1.33
Contribution to Project: Worked with Dr. Matthay to write and edit the Clinical Protocol and the Investigator Brochure, and to edit the case report form and to set up the cIRB with Vanderbilt for this trial.

Serena Ke, BS
Project Role: Coordinator
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 9.58
Contribution to Project: Worked on preparing the clinical protocol, case report form and screening form for the trial and also the laboratory and study manuals for the trial.

Brian Daniel
Project Role: Coordinator
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 1.19
Contribution to Project: Worked on the clinical protocol and case report form development.

Kevin Delucchi, BS, PhD
Project Role: Statistician
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 0.98
Contribution to Project: Prepared the statistical plan for the clinical protocol that was submitted to FDA. Helping to revise the statistical plan with more details.

Shibani Pati, MD, PhD
Project Role: Co-Investigator0000-0001-2345-6789
Nearest person month worked: 0.86
Contribution to Project: Working on standardizing laboratory assays for the MSCs for this trial including plans to test the viability and other features of the bone marrow derived MSCs from the University of Minnesota.

Jason Abbott, BS
Project Role: Laboratory Manager
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 2.08
Contribution to Project: Organizing specimen tubes and bar coding for this trial

Xiaohui Fang
Project Role: Specialist (laboratory)
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 0.20
Contribution to Project: Funcitonal assays of mesenchymal stromal cells.

Stuart Gibb, PhD
Project Role: Research assistant
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 0.45
Contribution to Project: Working with Dr. Pati on standardizing laboratory assays for the MSCs for this trial

Alpa Mahuvakar
Project Rose: Research assistant
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 2.34
Contribution to Project: Worked with Dr. Pati on laboratory assays for the MSCs for this trial.

Maribeth Ruperto
Project Role: Post award grant manager
Research Identifier: 0000-0001-2345-6789
Nearest person month worked: 0.55
Contribution to Project: Worked with Dr. Matthay for organizing the personnel contributions to this grant and preparing the quarterly report.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? –** The PI is Dr. Matthay and his updated Other Support is attached to this report as an Appendix.

- **What other organizations were involved as partners?** Nothing to report.

8. **SPECIAL REPORTING REQUIREMENTS:**

- **COLLABORATIVE AWARDS:** Not applicable.
- **QUAD CHARTS:** Not applicable.

9. **APPENDICES:** Nothing to report.

SUPPORT
MATTHAY, MICHAEL A.

Current
Title: Resolution of Clinical Lung Injury
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NHLBI, R37 HL051856
Address:
NIH/NHLBI Information center
P.O Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Charmaine Prasad
Performance Period: 04/01/2011-03/31/2017
Level of funding: $263,019
Project Goals: To study the pathogenesis of acute lung injury and ARDS, with an emphasis on alveolar epithelial fluid clearance, through the use of clinical studies.
Specific Aims: The specific aims are to study the the pathogenetic and prognostic value of biomarkers in patients with ARDS, to test the effect of human edema fluid from ARDS patients in both an in vitro model of cultured human alveolar epithelial type 2 cells and new therapeutics for acute lung injury in an isolated perfused human lung preparation.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Allogeneic Human Mesenchymal Stem Cells for the Treatment of Acute Lung Injury
Time Commitments: 1.2 calendar
Supporting Agency: NIH/NHLBI, U01 HL108713
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Kimberly Stanton
Performance period: 09/01/2011-06/30/2017
Level of funding: $1,587,045
Project Goals: To test the safety and efficacy of human mesenchymal stem cells for the treatment of severe acute lung injury.
Specific Aims: The specific aim is to test the therapeutic value of intravenous human bone marrow derived mesenchymal stem cells for the treatment of 60 patients with moderate to severe ARDS for safety and limited efficacy endpoints, using a 2:1 randomization with a double blind design. There is also an aim to study the biologic markers of injury that may be altered in the plasma and bronchoalveolar lavage in the placebo versus treated patients.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Prevention and Early Treatment of Acute Lung Injury
Time Commitments: 1.2 calendar
Supporting Agency: NIH/NHLBI, U01 HL123004
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Gayle Jones
Performance period: 6/17/2014-04/30/2021
Level of funding: $286,844

Project Goals: Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal
To test new treatments for acute lung injury in patients enrolled in the Emergency Department and in the Intensive Care Unit.
Specific Aims: The specific aim is to test new therapeutic approaches to testing the preventative or early treatment value of novel treatments in patients admitted to the Emergency Department at risk for ARDS or new treatments for ARDS in patients in the intensive care unit in primarily phase 3 designs.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Cigarette Smoke Exposure and Acute Lung Injury After Severe Blunt Trauma
Time Commitments: 0.30 calendar
Supporting Agency: NIH/NHLBI, R01 HL110969
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Charmaine Prasad
Performance period: 12/15/2011-11/30/2016
Level of funding: $250,000
Project Goals: To determine the biologic effects of cigarette smoke exposure that increase susceptibility to acute lung injury after severe trauma.
Specific Aims: The specific aim is to determine the effect of cigarette smoke on increasing the risk of ARDS in major trauma patients, including accounting for passive versus active cigarette smoke exposure and alcohol use. There is also one aim designed to test the relationship of the microbiome in the airways at baseline and on days 2-4 sampled by bronchoalveolar lavage to cigarette smoke exposure and to the development of ARDS in major trauma patients.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Identification of Patients at High Risk for the Development of ALI with Clinical and Biological Predictors
Time Commitments: Effort as needed
Supporting Agency: U Penn Subcontract/Glaxo Smith Kline, Galaxy ALI (subcontract)
Address:
Glaxo Smith Kline
709 Swedeland Road
King of Prussia, PA 19406
Contracting/Grants Officer: Susan Russell
Performance period: 06/26/2012-06/25/2016
Level of funding: $39,681
Project Goals: To identify clinical and biological predictors of ALI in a cohort of patients with sepsis
Specific Aims: The aim is to determine the biological predictors of ARDS in the plasma of sepsis patients in the Emergency department at risk for developing ARDS.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Quantification and Biomarkers of Short-Term Pulmonary Effects of Tobacco Smoke Exposure: Infection-Related Acute Lung Injury
Time Commitments: 0.60 calendar
Supporting Agency: NIH/FDA
NCI Contact Center
BG 9609 MSC 9760
9609 Medical Center Drive Bethesda, MD 20892-9760
Contracting/Grants Officer: Rebecca Brightful

Performance period: 09/01/2013-08/31/2018
Level of funding: $23,601
Project Goals: To quantify the association between cigarette smoke exposure and the development of acute lung injury in patients with severe infection and in mouse models of infection-related ALI, and to develop new biomarkers for tobacco-related acute lung injury
Specific Aims: The specific aims are to test the biological and clinical predictors of developing ARDS in patients at risk for developing ARDS who smoke cigarettes versus those who do not and identifying biomarkers that may be associated with the increased risk. One aim also tests the effects of cigarette smoke exposure in mice to determine if they are more susceptible to acute lung injury from endotoxin or bacterial lung infection.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: TIMP-3 For Viral Induced Acute Lung Injury
Time Commitments: 0.8 calendar
Supporting Agency: Amgen, 2013583306
Address:
Extramural Research Alliances (ERA)
Amgen, Inc.
One Amgen Center Drive Thousand Oaks, CA 91320
Contracting/Grants Officer: Scott Simonet
Performance period: 12/03/2013-12/02/2016 Level of funding: $174,275
Project Goals: To test a new therapy with TIMP-3 for influenza pneumonia and lung injury.
Specific Aims: To evaluate the potential therapeutic value of inhibiting TIMP-3 to reduce acute lung injury from PR8 H1N1 influenza in mice.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: The GOLD STUDY: Goal of open lung ventilation in donors
Time Commitments: 1.2 Calendar
Supporting Agency: NIH/NHLBI,R01HL126176
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Richard Steinheart
Performance period: 12/01/2014-11/30/2019
Level of funding: $99,102
Project Goals: Dr. Matthay's laboratory will be responsible for processing the human lungs collected and studied in Aim 2 of this application. Dr. Matthay himself will also oversee the conduct of the trial as described in Aim 1 in conjunction with Dr. Ware at Vanbderbilt.
Specific Aims: The specific aim is to test a higher level of positive end expiratory pressure (PEEP) 10 cmH20 versus a lower PEEP of 5 cmH20 to increase the rate of transplantation of lungs from brain dead donors in a randomized trial.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Gene-modified mesenchymal stem (stromal) cells for Treatment of the Acute Respiratory Distress Syndrome
Time Commitments: 0.3 calendar
Supporting Agency: UC/CAI grant, 20130924SFM
Address:
11000 Kinross Avenue, Suite 211 Los Angeles, CA 90051
Contracting/Grants Officer: Susan Waelder
Performance period: 03/01/2015-02/28/2017

Level of funding: $100,000
Project Goals: Our primary objective will be to carry out proof of principle studies to determine which combination of genes for KGF, Ang-1, and TIMP3 transfected into MSCs will produce the most therapeutically effective conditioned media (CM) for treating ARDS using pre-clinical models of pneumonia and sepsis in mice and severe pneumonia and lung injury in our novel ex vivo perfused human lung.
Specific Aims: Specific aim is to determine to potential therapeutic efficacy of an enriched conditioned media from transfected MSCs for reducing in vitro lung endothelial and epithelial injury and then test the conditioned media in an endotoxin model of lung injury in mice.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Molecular Endotypes of ARDS: Identification, Biology, and Differential Response to Therapy
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NHLBI R01 HL131621
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Sunshine Wilson
Performance Period: 04/01/2016-03/31/2020
Level of funding: $259,224
Project Goals: To identify endotype-specific treatment responses and differences in endotype biology within ARDS
Specific Aims: To test biologic and clinical variables in ARDS patients to identify clinically meaningful phenotypes that would be more specific for therapeutic targets.
Overlap: None

Pending
Title: Mesenchymal Stem Cell (MSC) or MSC Derived Factors for the Prolonged Field Care of Wounded Military Personnel with Traumatic Brian Injury and Hemorrhagic Shock
Time Commitments: 1.8 calendar
Supporting Agency: NIH
Address:
NIH
9000 Rockville Pike
Bethesda, MD 20892
Contracting/Grants Officer: Pending
Performance Period: 01/01/2017-12/13/2019
Level of Funding: $ 802,202
Project Goal: To conduct preclinical animal studies to test the efficacy of MSC derived factors, specifically lyophilized conditioned media from MSC, for treatment of traumatic brain injury in rats and pigs for application in prolonged field care as is currently done with lyophilized fresh frozen plasma in combat victims who are injured.
Specific Aims: Aim 1. To test lyophilized conditioned media of MSC for efficacy in cultured endothelial cells.Aim 2. To test the lyophilized conditioned media of MSC in a rat model of traumatic brain injury and Aim 3. To test the lyophilized conditioned media of MSC in a pig model of traumatic brain injury.
Overlap None

Previous
Title: Genetic risks for ALI in ARDSnet and the iSPAAR Consortium
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NHLBI RC2 HL101779/University of Washington

Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Michael Blackwell (University of Washington)
Performance Period: 9/30/2009-8/31/2012
Level of Funding: $50,000
Project Goal: To identify genetic factors contributing to the pathogenesis of ARDS.
Specific Aims: **To study DNA and plasma for biological factors that predict outcomes in ARDS patients.**
Overlap None

Title: Treatment of Pulmonary Edema in Organ Donors
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NHLBI R01 HL088263/VUMC (subcontract)
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Libby Salberg (VUMC)
Performance Period: 2/01/2008 -01/31/2013
Level of Funding: $11,982
Project Goal: To test aerosolized albuterol a beta agonist to improve lung function in brain dead subjects.
Specific Aims To carry out a randomized trial of inhaled albuterol versus placebo to increase lung utilization for lung transplantation.
Overlap None

Title: Sedation Management in Pediatric Patients with Acute Respiratory Failure
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NHLBI U01HL086622 /University of Pennsylvania (subcontract)
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Sheila R. Atkins (University of Pennsylvania)
Performance Period: 4/1/2008-3/31/2013
Level of Funding: $11,269
Project Goal: To test a sedation strategy to improve clinical outcomes in children with acute respiratory failure who were being mechanically ventilated.
Specific Aims: To use a cluster design to test a protocolized sedation strategy to increase ventilator free days in pediatric patients with acute respiratory failure.
Overlap: None

Title: Lung Fluid Balance and Mesenchymal Stem Cells
Time Commitments: 2.4 calendar
Supporting Agency: NIH/NHLBI R01HL051854
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Dianna Jessee (GMO)
Performance Period: 9/30/2008-6/30/2013
Level of Funding: $382,388

Project Goal: To study the mechanisms by which mesenchymal stem cells reduce lung injury in experimental models.
Specific Aims: To study the efficacy and mechanisms of mesenchymal stem cells in mouse models of acute lung injury.
Overlap : None

Title: Stromal stem cells of human placenta for the treatment of Acute Lung Injury
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NHLBI R43HL108327/Plasalus LLC
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Frans A Kuypers (Plasalus)
Performance Period: 8/1/12-5/31/2014
Level of Funding: $72,342
Project Goal: To test the efficacy of human placental mesenchymal stem cells for reducing lung injury in both in vitro and in vivo models of lung injury.
Specific Aims : To use human type 2 cells and the ex vivo perfused human lung preparation to test the efficacy of human placental stem cells for reducing lung injury from endotoxin.
Overlap None

Title: Clinical Research Network for the Treatment of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)
Time Commitments: 0.6 cal
Supporting Agency: NIH/NHLBI HHSN268200536166C
Address: NHLBI, NIH
Rockledge II building, Rm 6016
6701 Rockledge Drive MSC 7902
Bethesda MD 20892-7902
Contracting/Grants Officer: Scott Bredow (NHLBI)
Performance Period: 12/1/2011-6/30/2014
Level of Funding: $33,122
Project Goal:To test in phase 3 trials new treatments for acute lung injury and ARDS.
Specific Aims: To enroll patients in randomized clinical trials in the NHBLI ARDS Network.
Overlap: None

Title: Metabolic Response to Acute Injury in Alveolar Epithelium and ARDS
Time Commitments: 0.12 calendar
Supporting Agency: Stanford /American Thoracic Society, 60995841-117524
Address:
Stanford University Office of Sponsored Research 3160 Porter Drive, Suite 100
Palo Alto, CA 94304-8445
Contracting/Grants Officer: Teresa Tom
Performance Period: 11/30/14-11/29/15
Level of Funding: $10,000
Project Goal: To study the metabolic factors released by human alveolar epithelial type 2 cells in culture and to supply pulmonary edema fluid for metabolomics studies.
Specific Aims: The specific aim is to determine the metabolic abnormalities that may have pathogenetic or prognostic significance in cultured human epithelial type 2 cells exposed to cytomix (pro-inflammatory stimulus) and to test the metabolic abnormalities in undiluted edema fluid from patients with hydrostatic versus

acute lung injury (ARDS).
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: Gene-modified mesenchymal stem (stromal) cells for Treatment of the Acute Respiratory Distress Syndrome **A125202**
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NHLBI U54HL119893/UCLA
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Mary Haskins (UCLA)
Performance Period: 3/1/15-2/29/2016
Level of Funding: $100,000
Project Goal: Our primary objective will be to carry out proof of principle studies to determine which combination of genes for KGF, Ang-1, and TIMP3 transfected into MSCs will produce the most therapeutically effective conditioned media (CM) for treating ARDS using pre-clinical models of pneumonia and sepsis in mice and severe pneumonia and lung injury in our novel ex vivo perfused human lung.
Specific Aims: Specific aim is to determine to potential therapeutic efficacy of an enriched conditioned media from transfected MSCs for reducing in vitro lung endothelial and epithelial injury and then test the conditioned media in an endotoxin model of lung injury in mice.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal

Title: The inflammasome: A Novel Biomarker in ALI/ARDS
Time Commitments: .12 calendar
Supporting Agency: NIH/NHLBI R01 HL112747/Brigham & Women's Hospital
Address: NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Stephanie Redfield (Brigham & Women's Hospital)
Performance Period: 5/15/2012-4/30/2016
Level of Funding: $6,577
Project Goal: To determine the predictive value of biomarkers of the inflammasome in acute lung injury.
Specific Aims: To test the predictive value of plasma levels of biomarkers of the inflammasome on developing ARDS in at risk patients plus to determine the modifying effect if any on these biomarkers of treatment with statins.
Overlap: None

Title: Recipient Epidemiology and Donor Evaluation Study-III *REDS-III) –Domestic Sites
Time Commitments: 1.8 calendar
Supporting Agency: NIH/NHLBI, HHSN268110005I
Address:
NIH/NHLBI Information center
P.O Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: Michael Spears
Performance period: 03/15/2011-08/31/2016
Level of funding: $637,636
Project Goals: To assure safe and effective blood banking and transfusion medicine practices through a comprehensive, multi-targeted strategy involving basic, translational, and clinical research to improve the benefits of transfusion while reducing its risks.
Specific Aims: The specific aim is to test clinical criteria for determining if patients who have blood product

transfusions who develop pulmonary edema have TACO or TRALI or ARDS from a usual risk factor (not blood products) by reviewing specific patient cases from three hospitals with a consensus panel.
Overlap: No scientific or budgetary overlap with the proposed PRMRP proposal