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: The Regents of the University of California
San Francisco, CA

REPORT DATE: October 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command Fort
Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE		Form Approved OMB No. 0704-0188
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of		
1. REPORT DATE October 2021	**2. REPORT TYPE** Annual	**3. DATES COVERED** 15Sep2020-14Sep2021
4. TITLE AND SUBTITLE Mesenchymal Stem Cells for Treatment of ARDS Following Trauma		**5a. CONTRACT NUMBER** W81XWH-17-1-0631 **5b. GRANT NUMBER** **5c. PROGRAM ELEMENT NUMBER**
6. AUTHOR(S) Michael Matthay E-Mail: Michael.Matthay@ucsf.edu		**5d. PROJECT NUMBER** **5e. TASK NUMBER** **5f. WORK UNIT NUMBER**
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Regents of the University of California, San Francisco 3333 California Street, 315 San Francisco, CA 94143		**8. PERFORMING ORGANIZATION REPORT NUMBER**
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		**10. SPONSOR/MONITOR'S ACRONYM(S)** **11. SPONSOR/MONITOR'S REPORT NUMBER(S)**
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited		
13. SUPPLEMENTARY NOTES		

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 whichMSC reduce acute lung injury in patients with ARDS.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	30	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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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. 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. Subsequently emerging evidence suggests that the incidence of ARDS following trauma has declined, probably related to changes in resuscitation practices with the reduced use of crystalloid fluids and balanced transfusion of blood products. In order to study all patients with ARDS after trauma as well as to meet enrollment goals over the defined study period, after the discussion with the Department of Defense, the inclusion criteria for this phase 2b trial were broadened before the trial was started to include all causes of ARDS for testing MSCs for both trauma and medical causes of ARDS.

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

3. ACCOMPLISHMENTS:

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

During Year 4, our major goals were as follows:

1. Expand site activation and enrollment at Vanderbilt University Medical Center, University of California Davis and University of Washington Harborview Medical Center
2. Continue to recruit patients at all seven participating sites.
3. Revise the protocol with changes in the inclusion and exclusion criteria
4. Submissions to single IRB at VUMC, which mainly the following tasks: (1) Renewed the trial; (2) Submit a protocol amendments regarding minor inclusion/exclusion revision; (3) Local consent context revisions due to personnel (not site PI) changes; (4) FAQ revisions
5. Submit IND amendment and annual progress report to the FDA under IND 15331
6. Submit study renewal and protocol amendment to the DoD HRPO to obtain the DoD approvals
7. Each site to finalize their site-specific MSC preparation and MSC infusion protocol, based

on the approved MSC preparation and infusion protocol which are included in the current Clinical Protocol

8. Hold DSMB teleconference in May 2021 to review all safety data and interim analysis for the first 60 patients
9. Hold monthly teleconference with the study investigators and study coordinators at all participating sites.
10. Training of coordinators and investigators with a conference call and meetings by conference call. Webinar educational sessions to introduce the data management system to investigators, BMT staff (randomization) and study coordinators.

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

Goal #1: Expand site activation and enrollment at Vanderbilt University Medical Center, University of California Davis and University of Washington Harborview Medical Center – Completed

During the past reporting period, we have opened three participating sites that are listed below:

- VUMC – Screening initiated in November 2020
- UCD – Screening initiated in December 2020
- Harborview (UW) – Screening initiated in February 2021

All participating sites have completed their regulatory requirements and study product quality control reviews and have been granted site activation. The University of Minnesota MSC production site is responsible for the production of the clinical-grade MSCs and supports all 7 participating sites. The necessary testing at local sites and their results were required to be reviewed by Overall PI, Dr. Michael Matthay prior to the initiation of the trial.

Goal #2: Continue to recruit patients into the trial at 7 participating sites

Currently all 7 sites are actively recruiting patients into the trial. As of October 12, 2021, we have enrolled a total of 97 patients into the trial, including

14 patients at UCSF,
36 patients at ZSFG,
14 patients at OHSU,
10 patients at UTHSCH,
8 patients at Vanderbilt University Medical Center
8 patients at UC Davis
7 patients at UW-Harborview Medical Center

Of the 97 patients, 83 patients were COVID-19 positive. All 97 patients completed the study product infusion without interruption.

One safety report was submitted to the FDA (MedWatch: Patient Identifier: IND15331-504) on February 5, 2021, and reported to the DoD through the 14th quarterly technical report dated March 29, 2021.

In brief, this was an 84-year-old female patient who initially presented to her PCP for progressive weakness and was referred to the ER and admitted for treatment of Enterococcus faecalis

bacteremia, hypokalemia, AKI (creatinine 1.51), and paroxysmal atrial fibrillation. During the hospitalization, the patient was diagnosed with septic shock due to E. faecalis endocarditis/pacemaker infection and developed acute respiratory distress syndrome. The patient was enrolled in the clinical trial and the study product was administered. No reactions were noted during the infusion. A CT of the abdomen was ordered to be performed after study product infusion for concerns of on-going sepsis, persistent fever, and possible abscess. When the patient remained obtunded in the afternoon despite discontinuation of sedatives, a CT of the head was added on for further evaluation. The CT of the abdomen was unremarkable. The CT of the head was completed approximately 2 hours after completion of study product infusion and revealed evidence of recent left occipital ischemia. Differential diagnosis for the new CT findings from neurologic consultants included paradoxical emboli, sepsis-induced hypercoagulation, hypoperfusion, and secondary vasculitis. In that evening, the patient deteriorated and was transitioned to comfort care and passed on the next day and the cause of death was thought to be septic shock due to E. faecalis endocarditis/pacemaker infection and was not related to the study product infusion.

Per the IRB approved Clinical Protocol, any cardiac arrest or death that occurred within 24 hours from the start of study product would be reported as a pre-specified, infusion-associated significant event, we then reported this serious adverse event to Dr. Taylor Thompson (Medical Monitor and the Chair of the DSMB) and the single IRB at Vanderbilt University. Dr. Thompson concurred that the death was unlikely to be related to the investigational product/placebo for the reasons outlined in the comprehensive narrative. The occipital infarction almost certainly predated the study infusion and this patient was at high risk for such an event (CNS emboli from right sided endocarditis with right to left shunt) and the protocol specified inline IV filter was used. The IRB Committee has accepted the reported Adverse Event and determined the event does not constitute an Unanticipated Problem Involving Risk to Participants or Others and that no changes to the protocol or consent form(s) are needed at this time.

Goal #3: Revise the protocol with changes in the inclusion and exclusion criteria – completed

During the past reporting year, we have amended the Clinical Protocol once, and we have also updated the related study documents for this Phase 2b trial listed as below:

Clinical Protocol:

The Clinical Protocol has been revised regarding inclusion and exclusion criteria in May 2021 (Protocol No: UCSF-hMSC-ARDS-P1P2-13, dated May 21, 2021). These minor changes include:

- The enrollment window has been changed from within 120 hours of initial ICU admission to within 14 days of initial ICU admission. By increasing the enrollment window up to 14 days, we want to increase the opportunity to recruit more medical and surgical patients into this trial.
- We have removed the exclusion criteria #23: Received tocilizumab within the last 7 days. Tocilizumab treatment has become a standard care at several of our participating STAT hospitals for patients with COVID-19. So it is not feasible to exclude any patients who received tocilizumab within the last 7 days.

Investigator Brochure:

The Investigator Brochure has been updated to reflect the changes of the Clinical Protocol. During the past reporting year, we developed one newer version of Investigator Brochure: Version 13 (dated May 21, 2021, current version).

Informed Consent Form (ICF):

We are using the Vanderbilt IRB as the single IRB (sIRB) at Vanderbilt University Medical Center (VUMC) for this Phase 2b trial. Per the Vanderbilt IRB's guidelines, the consent forms at each site includes two parts: main consent (Part 1) to be used for all seven sites, and local consent context form (Part 2) which has site-specific language.

The main consent has not been changed and the current version 1.5 was dated June 24, 2020. This main consent form has also been translated into Spanish and Russian, and approved by the sIRB and will valid till March 3, 2022.

All recruitment sites have developed site-specific consent forms. The local consent forms for all 7 participating sites have been approved by the sIRB at VUMC and the Department of Defense. During the past year, we have made some minor changes regarding contact information (non-PI) for University of Texas Health Science Center at Houston. The current versions of the local consent context forms (Part 2) for all sites are listed as below:

- University of California San Francisco (UCSF): dated 04/03/2020
- Zuckerberg San Francisco General Hospital & Trauma Center (ZSFG): dated 02/24/2020
- University of Texas Health Science Center at Houston (UTHSCH): dated 09/30/2021
- University of Washington, Harborview Medical Center (Harborview): dated 04/22/2021
- Oregon Health & Science University (OHSU): dated 04/03/2020
- Vanderbilt University Medical Center (VUMC): dated 04/03/2020
- University of California Davis (UCDavis): dated 06/03/2020

Case Report Form (CRF):

We have updated the case report forms to reflect the new changes in the Clinical Protocol. The current version is dated May 24, 2021.

Statistical Analysis Plan (SAP):

We have updated the Statistical Analysis Plan to reflect the new changes in the Clinical Protocol. The current version is dated May 24, 2021.

Goal #4: Submissions to single IRB at VUMC, which mainly the following tasks: (1) Renew the Phase 2b clinical trial; (2) Submit a protocol amendment regarding minor inclusion/exclusion revision; (3) Local consent context revisions due to personnel changes (not site PI); (4) FAQ revisions – completed.

The central IRB at Vanderbilt University Medical Center (PI – Todd Rice, MD) is the central IRB, and all 7 sites (UCSF, ZSFG, OHSU, UTHSCH, Harborview, OHSU, VUMC, UCD) have agreed to this plan and obtained the reliance approval from their institutional IRBs. The UCSF IRB is responsible for the regulatory issues for two recruitment sites: UCSF and ZSFG.

During the past reporting period, we have conducted the following regulatory activities with the central IRB at Vanderbilt University:

1. **IRB Amendment 13:** **Submission date:** 12/11/2020 **Approval date:** 12/19/2020

   Description: We submitted the revised local consent document for UTH to update the emergency contact personnel and her phone number.

2. **IRB Amendment 14:** **Submission date:** 12/22/2020 **Approval date:** 12/30/2020

   Description: We submitted translated Bill of Rights in Hungarian which was used as translated short consent form at UCSF and ZSFG.

3. **IRB Renewal:** **Submission date:** 02/15/2021 **Approval date:** 03/04/2021

   Description: We submitted the IRB renewal request to the sIRB at VUMC for all 7 sites: UCSF, ZSFG, UTHSCH, Harborview, OHSU, VUMC and UCD. The new IRB expiration date is March 3, 2022.

4. **IRB Amendment 15:** **Submission date:** 04/30/2021 **Approval date:** 05/06/2021

   Description: We submitted the revised local consent document for Harborview Medical Center to update the emergency contact personnel and the contact phone number.

5. **IRB Amendment 16:** **Submission date:** 05/25/2021 **Approval date:** 06/10/2021

   Description: We submitted the IRB amendment for the following changes: (1) Updated Clinical Protocol with Protocol Amendment 3 regarding minor changes in inclusion and exclusion criteria; (2) Updated IRB application form to reflect inclusion/exclusion criteria changes in the Clinical Protocol; (3) Updated Investigator Brochure to reflect the minor protocol revision; (4) Submission of FAQ Set 2 regarding the adjustment for COVID-19 pandemic and the clarification of Clinical Protocol; (5) Submitted the updated Statistical Analysis Plan to reflect the protocol changes; (6) Submitted the updated Case Report Form; (7) Submitted DSMB recommendation letter dated 05/17/2021.

6. **IRB Amendment 17:** **Submission date:** 08/31/2021 **Approval date:** 09/02/2021

   Description: We submitted an updated FAQ (#3) to clarify the enrollment and study product infusion window.

7. **IRB Amendment 18:** **Submission date:** 10/01/2021 **Approval date:** 10/12/2021

   Description: We submitted the revised local consent document for UTH to update the emergency contact personnel and her phone number and currently is under sIRB's review.

Goal #5: Submit IND amendment and annual progress report to the FDA under IND 15331 – completed

During the past reporting year, we have submitted the two IND amendments to the FDA for this trial. Please note that no formal approval notices were required for these submissions.

1. **IND 15331 #0025:** **Submission date:** 03/09/2021

   This IND amendment submission included the following tasks and updates:
   - Submission of Annual Progress Report for the past year.
   - Submission of the Information Amendment for the updated key personnel list for 7 sites and research laboratory facilities.

2. **IND 15331 #0026:** **Submission date:** 05/26/2021

   This IND amendment submission included the following tasks and updates:
   - Submission of amended Clinical Protocol (Version 13).
   - Submission of revised Investigator Brochure and Statistical Analysis Plan.
   - Submission of DSMB recommendation letter (dated May 17, 2021)

We also submitted one safety report to the FDA (MedWatch: Patient Identifier: IND15331-504) on February 5, 2021, and reported to the DoD through the 14th quarterly technical report dated March 29, 2021 (see more details on page 5, Goal #2 Section).

*Please note that IND amendment #0023 and #0024 were email communications for inquiries which were not reportable.

Goal #6: Submit study renewal and protocol amendment to the DoD HRPO to obtain the DoD approvals – Completed

During the past reporting period, we have had the following communications with the DoD:

1. **Continuing Renewal:** On March 15, 2021, we submitted the Continuing Review Submission Forms and the supporting documents for 7 participating sites (UCSF, ZSFG, UTHSCH, Harborview, OHSU, VUMC and UCD). We received the DoD renewal approval by email on May 27, 2021.

2. **Protocol Amendment 3 – All sites**: The IRB amendment regarding Clinical Protocol Amendment 3 was approved by the sIRB at VUMC on June 10, 2021. On June 14, 2021, we submitted the following approved study documents to the DoD HRPO:

   Global study documents for all sites:
   - IRB submission form and IRB approval notice;
   - Clinical Protocol (Version 13, dated 05/21/2021) and Protocol Amendment 3 listing all proposed protocol changes;

- Updated Investigator Brochure (Version 13, dated 05/21/2021);
- Revised Case Report Form (dated 05/24/2021);
- Updated Statistical Analysis Plan (dated 05/24/2021);
- FAQ set 2 (dated 06/01/2021);
- DSMB Recommendation Letter (dated 05/17/2021)

The DSMB HRPO officer reviewed this protocol amendment submission and determined that this did not require HRPO oversight and approved us to proceed with implementing the changes (email communication dated June 28, 2021).

Goal #7: Each site to finalize their site-specific MSC preparation and MSC infusion protocol, based on the approved MSC preparation and infusion protocol which are included in the current Clinical Protocol. – Completed

Each site should have developed site-specific study product preparation SOP and infusion SOP, based on the IRB-approved SOP template (in Clinical Protocol Appendices E and H). All 7 sites (UCSF, ZSFG, OHSU, UTHSCH, VUMC, Harborview and UCD) have completed site-specific SOP development regarding study product preparation and study product infusion and approved by the CCC at UCSF before site activation.

Goal #8: Hold DSMB teleconference in May 2021 - completed.

We passed our enrollment target for the interim DSMB safety review for the first 60 patients. The 60th patient was randomized on January 28, 2021 and all 60 patients have completed study follow-up up to 60 days.

The interim DSMB meeting was held on May 17, 2021. Materials submitted to the DSMB for review included the protocol summary, statistical analysis plan, interim safety analysis involving 60 participants, and the narratives for deaths. After the thorough review and discussion during the meeting, the DSMB recommended that the trial should continue. The Board accepted the investigator's recommendation to remove the tocilizumab exclusion criteria and to modify exclusion criteria to extend the duration of ICU admission greater than 14 days.

Goal #9: Monthly teleconference with the study investigators and study coordinators at all participating sites – Completed.

We have held regular one-hour monthly teleconferences with the study investigators, study coordinators and Stem Cell Lab personnel at all participating sites (second Tuesday of every month) for study progress updates and the discussions related to this trial. The Science Officer of the DoD has been invited to attend this teleconference.

Meanwhile, weekly emails regarding study progress have been sent to all STAT research personnel. Our study website (www.stattrial.com) have been continuously updated to provide enrollment tracking, study documents (e.g. protocol , Investigator Brochure, Consent forms, Case Report Forms et al.) and regulatory approval documents.

Goal #10: Training of coordinators and investigators with meetings by conference call. Webinar educational sessions to introduce the data management system to investigators, BMT staff (randomization) and study coordinators – Completed

We have provided the study initiation training for all the participating sites. We have provided constant consultation by phone calls (especially to the PI, Dr. Matthay) and emails for any research related questions. We have also distributed the study related documents and SOPs to help each participating site to initiate the study recruitment. We have developed three separate User Manuals to provide step-by-step instruction for: (1) E-consent portal through VUMC REDCap; (2) Study randomization portal through QuesGen system; (3) Data entry portal through QuesGen system. We have also created the mock databases for each user so they can practice and be familiar with the systems. The CCC at UCSF and QuesGen team is available for consultation at any time. We will continue to provide necessary training and consultation to facilitate the study conduction.

- **What opportunities for training and professional development has the project provided?** Carolyn Hendrickson, MD, MAS and Lucy Kornblith, MD, MAS have become proficient at leading a challenging clinical trial including screening, consent, enrollment and overseeing all of the details of the trial at ZSFG. They are both Assistant Professors so this is an excellent professional development experience for them. Both Drs. Hendrickson and Kornblith have NIH K awards and Dr. Matthay is their primary mentor.
- **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?**
  1. Continue to recruit patients into the study to reach the enrollment target of 120 patients
  2. Continue to provide education and support for study conduct at all sites
  3. Hold a 6-month DSMB teleconference in November to December 2021 for safety review

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**

1. **Protocol Amendment 3 (dated 05/17/2021) included the following changes, and all of them were considered as minor revisions.**
   i. Increase enrollment window from 120 hours to 14 days since the initial ICU admission
   ii. Remove the exclusion criteria for patients with recent tocilizumab treatment

- **Actual or anticipated problems or delays and actions or plans to resolve them - None**

- **Changes that had a significant impact on expenditures - None**

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

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

6. **PRODUCTS:**
   - **Publications, conference papers, and presentations:** Nothing to report.
   - **Website(s) or other Internet site(s):** www.stattrial.com
   - **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?**

UCSF - UCSF Moffitt-Long Hospital and Zuckerberg San Francisco General Hospital & Trauma Center (San Francisco, CA):
Michael A. Matthay MD
Project Role: Principal Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 4.00
Contribution to Project: Revised the FDA approved Clinical Protocol and Investigator Brochure for submission to the Vanderbilt cIRB; communicated with all of the sites (6 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 and by conference call (November 30, 2018 – Tal Salz, CBER); communicated with the Dave McKenna, MD at the University of Minnesota regarding details for production of the mesenchymal stromal cells for the trial; worked on selecting the DSMB for the trial.

Kathleen D. Liu, MD, PhD, MAS
Project Role: Co-Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.36
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 Zhuo, the project manager. Dr. Liu also worked Melanie McMillan and Lizette Caballero on finalizing the laboratory SOPs for preparing the MSC and placebo infusion products. She is available to oversee study product infusion in the Parnassus ICU.

Carolyn Calfee, MD MAS
Project Role: Co-Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.68
Contribution to Project: Worked with Dr. Matthay on editing the clinical protocol, the screening form, and Case Report Form and overseeing delivery of study product to patients in the UCSF Parnassus ICU. She is also on the consent team.

Carolyn Hendrickson, MD, MAS
Project Role: Co-Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 1.07
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. She is the primary site investigator at ZSFG and is Medical Director of the ZSFG Medical ICU.

Hanjing Zhuo, MD, MPH
Project Role: Project Manager
Research Identifier 0000-0003-3039-8155:
Nearest person month worked: 0.0
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. She is the primary Project Manager for this STAT trial and works closely with Dr. Matthay.

Kevin Delucchi, BS, PhD
Project Role: Statistician
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.15
Contribution to Project: Prepared the statistical plan for the clinical protocol with attention to the FDA-requested expansion of the statistical plan with more details.

Shibani Pati, MD, PhD
Project Role: Co-Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.82
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.

Xiaohui Fang
Project Role: Laboratory analysis of MSCs for viability and functional characteristics
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.30
Contribution to Project: Testing properties of MSCs with in vitro assays and potency assays

Alpa Mahuvakar
Project Role: Research assistant
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.60
Contribution to Project: Worked with Dr. Pati on laboratory assays for the MSCs for this trial.

Haoqian, Zhang
Project Role: Specialist 2
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 4.32
Contribution to Project: Worked to characterize all clinical doses from the MSC Trial.

Dennis Hua
Project Role: Post award grant manager
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 1.20
Contribution to Project: Worked with Dr. Matthay for organizing the personnel contributions to this grant and preparing the quarterly report.

Nguyen Viet
Project Role: Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 09.35
Contribution to Project: Prepare and test the screening forms and practicing obtaining consents with Dr. Matthay.

Wick, Katherine Desprez
Project Role: Post Doctoral fellow
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 1.0
Contribution to Project: Helped to plan the biology studies

Kornblith, Lucy
Project Role: Co-PI
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.43
Contribution to Project: Screened, consented and enrolled patients in the trial

Ashktorab Kimia
Project Role: Clinical Research Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 04.19
Contribution to Project: Worked on preparing the case report form and screening form for the trial and the laboratory and study manuals for the trial.

Gropper Rachael
Project Role: Clinical Research Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 3.30
Contribution to Project: Worked on preparing the case report form and screening form for the trial and the laboratory and study manuals for the trial.

Vivona Lindsay Rae
Project Role: Laboratory research
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 1.88
Contribution to Project: Worked on the MSC biology studies

Agrawal Anika
Project Role: Clinical Research Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 2.53
Contribution to Project: Worked on preparing the case report form and screening form for the trial and the laboratory and study manuals for the trial.

Ambachew, Biniam M
Project Role: Clinical Research Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.93
Contribution to Project: Worked on preparing the case report form and screening form for the trial and the laboratory and study manuals for the trial

University of Harborview Medical Center (Seattle, WA)
Bryce Robinson, MD
Project Role: Site Principal Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.60
Contribution to Project: communicated with overall PI, Michael A. Matthay, MD and Clinical Coordinating Center at UCSF by conference calls and by emails and phone calls; supervised the reliance to a central IRB at Vanderbilt, and the preparation of site-specific regulatory documents for submission to the central IRB at Vanderbilt University, the FDA and the Sponsor, the Department of Defense.

Oregon Health & Science University (Portland, OR)
Martin Schreiber, MD
Project Role: Site Principal Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.60
Contribution to Project: communicated with overall PI, Michael A. Matthay, MD and Clinical Coordinating Center at UCSF by conference calls and by emails and phone calls; supervised the reliance to a central IRB at Vanderbilt, and the preparation of site-specific regulatory documents for submission to the central IRB at Vanderbilt University, the FDA and the Sponsor, the Department of Defense.

University of Texas Health Sciences Center at Houston/Memorial Hermann (Houston, TX)
Laura Moore, MD
Project Role: Site Principal Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.60
Contribution to Project: communicated with overall PI, Michael A. Matthay, MD and Clinical Coordinating Center at UCSF by conference calls and by emails and phone calls;

supervised the reliance to a central IRB at Vanderbilt, and the preparation of site-specific regulatory documents for submission to the central IRB at Vanderbilt University, the FDA and the Sponsor, the Department of Defense.

Vanderbilt University Medical Center (Nashville, TN)
Lorraine Ware, MD
Project Role: Site Principal Investigator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 0.60
Contribution to Project: communicated with overall PI, Michael A. Matthay, MD and Clinical Coordinating Center at UCSF by conference calls and by emails and phone calls; supervised the reliance to a central IRB at Vanderbilt, and the preparation of site-specific regulatory documents for submission to the central IRB at Vanderbilt University, the FDA and the Sponsor, the Department of Defense.

- **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 included in this report.

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

8. SPECIAL REPORTING REQUIREMENTS:

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

9. **APPENDICES:**

1. DoD (STAT) trial DSMB recommendation (dated May 17, 2021)

2. Active other support of the PI: Michael A. Matthay, MD

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Pulmonary and Critical Care Unit
55 Fruit Street, Bulfinch 148
Boston, Massachusetts 02114-2696
Tel: 617.724.9674, Fax: 617.726.6878
e-mail: thompson.taylor@mgh.harvard.edu

Boyd Taylor Thompson M.D.
Medical Director, PETAL CCC
Director, Translational Research
Division of Pulmonary and Critical Care Medicine,
Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

DoD (STAT) Trial DSMB Recommendations
May 17, 2021

DSMB Members Present:
B. Taylor Thompson, MD, DSMB Chair
Jason Sperry, MD, MPH
Michael Harhay, PhD

Dear Dr. Matthay,

Materials submitted to the DSMB for review included the protocol summary, statistical analysis plan, interim safety analysis involving 60 participants, and the narratives for deaths.

Following the discussion in the open session, the DSMB met in a closed session.

Recommendations:

1) The study should continue
2) The Board accepts the investigator's recommendation to remove the tocilizumab exclusion criteria (exclusion criterion #27)
3) The Boards accepts the investigator's recommendation to modify exclusion criterion #3 to extend the duration of ICU admission greater than 14 days

Respectfully Submitted,

B. Taylor Thompson MD
Chair, DoD (STAT) Trial DSMB

SUPPORT
MATTHAY, MICHAEL A.

Current

Title: *Prevention and Early Treatment of Acute Lung Injury*
Time Commitments: *0.45 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: *Direct Cost*
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: Mesenchymal Stem Cells for Treatment of ARDS Following Trauma
Time Commitments: 4.60 Calendar
Supporting Agency: *Department of Defense W81XWH-17-1-0631*
Address:
US Army Medical Research Acquisition Activity
820 Chandler ST
Fort Detrick MD 21702-5014
Contracting/Grants Officer: *Kevin R. Moore*
Performance Period: *9/15/2017-9/14/2021*
Level of funding: *Direct Cost*
Project Goals: The overall objective of this proposal is to carry out a randomized, double-blind, placebo-controlled multicenter phase 2b trial to test the therapeutic potential of allogenic bone-marrow derived MSC for treating ARDS in trauma patients.
Specific Aims: ***Specific Aim 1.*** To test the clinical efficacy of intravenously delivered allogeneic human MSC in trauma patients with ARDS. ***Specific Aim 2***. To test the mechanisms by which MSC reduce acute lung injury in trauma patients with ARDS
Overlap: *None*

Title: Novel Paracrine Mechanism for Cell-Based Therapy of Injured Lungs
Time Commitments: 0.45 Calendar
Supporting Agency: *University of Texas Health Science Center at Tyler/NIH R01 HL134828*
Address:
University of Texas Health Science Center at Tyler
11937 U.S. Highway 271
Tyler, TX 75708-3154
Contracting/Grants Officer: *Dena Walton*
Performance Period: *9/1/2017-8/31/2021*
Level of funding: *Direct Cost*
Project Goals: The results of these experiments will provide novel insights into how mesenchymal stem (stromal) cells enhance the resolution of alveolar edema in human lungs harvested from brain dead donors, an important scientific and clinical question.
Overlap: *None*

Title: Piceantannol entrapped albumin nanoparticles (PANPs) to combat ALI/ARDS
Time Commitments: 0.12 Calendar
Supporting Agency: Nano Biotherapeutics / NIH
Address:
Cell Biologics, Inc
2201 W Campbell Park Dr
Chicago, IL 60612
Contracting/Grants Officer: Jeanne Chang
Performance Period: 09/15/2017-06/30/2021 (NCE)
Level of funding: Direct Cost
Project Goals: This project is being done at UCSF in order to carry out the goals of specific aim 3, which is to test the efficacy of picetannol, an anti-inflammatory compound that is prepared as part of entrapped albumin nanoparticles (PANPs), to treat acute lung injury that occurs in the acute respiratory distress syndrome.
Overlap: *None*

Title: Precision Medicine in the Acute Respiratory Distress Syndrome
Time Commitments: 0.12 Calendar
Supporting Agency: *NHLBI/R35HL140026 (Calfee)*
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: *Manda C Richards*
Performance Period: *1/16/18-12/31/2024*
Level of funding: *Direct Cost*
Project Goals: To identify molecular endotypes of ARDS with distinct clinical and biological profiles, including integration of environmental exposure data and identification of differential treatment responses; to develop practical models for endotype identification; and to test biological mechanisms in an experimental human lung model.
Role: Co-Investigator
Overlap: *None*

Title: Angiopoietin/Tie signaling regulation of vascular leakage in lung inflammation
Time Commitments: 0.15 Calendar
Supporting Agency: *NHLBI/R01 HL143896 (McDonald)*
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer: *Tammi Simpson*
Performance Period: *7/1/2018-5/31/2022*
Level of funding: *Direct Cost*
Project Goals: To determine the contributions of angiopoietin-1(Ang1) and angiopoietin-2 (Ang2), and their receptors, Tie1 and Tie2 (Tek), to the regulation of vascular leak in lung injury and inflammation.
Role: Co-Investigator
Overlap: *None*
Title*: Integrated Health, Behavioral and Economic Research on Current and Emerging Tobacco Products*
Time Commitments: *0.12 Calendar*
Supporting Agency: NIH/NHLBI, U54HL147127 (Glantz)
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer*: Judy Sint*

Performance period: *9/1/2013-8/31/2023*
Level of funding: *Direct Cost (Project 1: Calfee)*
Project Goals: To provide a comprehensive assessment of the impact of varying e-cigarette characteristics on acute lung injury by combining data from cell culture, mouse models, and humans, including testing different device and e-liquid characteristics
Role: Co-Investigator
Overlap: None

Title: *Aerosol Delivery of Surfactant for ARDS*
Commitments: *0.12 Calendar*
Supporting Agency: KAER Biotherapeutics Corp/NIH
Address:
926 S. Andreasen Dr., Ste 105
Escondido, California 92029
Contracting/Grants Officer: *Donovan B. Yeates (CEO)*
Performance Period: *9/15/2018-6/30/2020*
Level of Funding: *Direct Cost*
Project Goals: Dr. Matthay will continue to work closely with Dr. Yeates to advise him on the practical aspects of the KAER surfactant delivery device with 1-2 annual visits to KAER therapeutics in San Diego.
Overlap: *None*

Title*: ARREST RESPIRATORY FAILURE DUE TO PNEUMONIA (ARREST PNEUMONIA)*
Time Commitments: *0.45 Calendar*
Supporting Agency: NIH/Stanford University UG3HL14722
Address:
Stanford University
3172 Porter Drive
Palo Alto CA 94304
Contracting/Grants Officer*: Sharon Collum*
Performance period: *9/1/19-3/31/2024*
Level of funding: *Direct Cost*
Project Goals: Dr. Michael Matthay will serve as an Executive Committee Member providing expertise in the design and conduct of multicenter clinical trials in patients at risk for lung injury.
Overlap: No scientific or budgetary overlap.

Title*: Mesenchymal Stromal Cells for ARDS (COVID Positive and COVID negative)*
Time Commitments: *0.24 Calendar*
Supporting Agency: CIRM
Address:
1999 Harrison Street, Suite 1650
Oakland, CA 94612
Contracting/Grants Officer*: Doug Kearney*
Performance period: *7/1/20-6/30/2022*
Level of funding: *Direct Cost*
Project Goals: Support the addition of the University fo California at Davis as a clinical site for enrolling 20 patients from 2020 to 2022 into an ongoing phase 2B trial of Mesenchymal Stromal Cells (MSCs) for the treatment the actue respiratory distress syndrome (ARDS), including both COVID-19 positive and COVID-19 negative patients.
Overlap: No scientific or budgetary overlap.

Title: University of California, San Francisco (UCSF) CIRM Alpha Stem Cell Clinic
Time Commitments: 2.52 calendar
Supporting Agency: CIRM
Address:

1999 Harrison Street, Suite 1650
Oakland, CA 94612
Contracting/Grants Officer: Michael Worden
Performance Period: 10/1/2019-11/30/2021
Level of funding:
Project Goals To address these gaps and expand clinical trial activity in cell therapies, the specific aims for an Alpha Stem Cell Clinic at UCSF at the above locations will be designed to accelerate the temple of pre-award planning, clinical trial activation, patient accrual and trial completion, expand access to these therapies by under-represented populations with disorders in the Alpha Stem Cell Network, and to establish a disease team approach that promotes participation in the CIRM Alpha Stem Cell Network trials
Overlap: *None*

Title*: Integrated Health, Behavioral and Economic Research on Current and Emerging Tobacco Products*
Time Commitments: *0.12 Calendar*
Supporting Agency: NIH/NHLBI, U54HL147127 (Glantz)
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer*: Judy Sint*
Performance period: *9/1/2013-8/31/2023*
Level of funding: *Direct Cost (Supplemental Funds)*
Project Goals: To provide a comprehensive assessment of the impact of varying e-cigarette characteristics on acute lung injury by combining data from cell culture, mouse models, and humans, including testing different device and e-liquid characteristics
Role: Co-Investigator
Overlap: None

Title*: Task Order: Identifying Treatable Targets in ARDS*
Time Commitments: *0.48 Calendar*
Supporting Agency: Genentech
Address:
One DNA Way, Mail Stop 245C
South San Francisco, CA 94080
Contracting/Grants Officer*: Dana Tolari*
Performance period: *12/1/2019-12/31/2022*
Level of funding: *Direct Cost*
Project Goals:
Role: Co-Investigator
Overlap: None

Pending

Title: Molecular profiling of ARDS edema fluid: a window to an injured lung.
Commitments: 0.12 Calendar
Supporting Agency: Stanford/NIH
Address:
Stanford University
3172 Porter Drive
Palo Alto CA 94304
Contracting/Grants Officer: Anitra Johnson
Performance period: 4/1/2020-3/31/2021
Level of funding: Direct Cost
Project Goals: We will deliver clinical data and biologic data on 20 patients with ARDS each year to be included in the studies and analyses that Dr. Rogers will do on mechanisms of acute lung injury in ARDS.

Overlap: No scientific or budgetary overlap. If all the pending applications are funded, the PI will adjust his efforts accordingly to stay in compliance.

Title: ENaC-α mediates lung fluid clearance and capillary barrier function in pneumonia
Commitments: 0.19 Calendar
Supporting Agency: Augusta University/ NIH
Address:
1120 15th Street
Augusta, GA 30912
Contracting/Grants Officer: Sandy Ferguson
Performance period: 7/1/2020-6/30/2020
Level of funding: Direct Cost
Project Goals: The experiments in the ex vivo perfused human lung preparation will provide valuable data for evaluating the efficacy of these agonists of sodium transport and barrier function in a clinically relevant model of bacterial pneumonia in the ex vivo perfused human lung.
Overlap: No scientific or budgetary overlap. If all the pending applications are funded, the PI will adjust his efforts accordingly to stay in compliance.

Title: Novel small-molecule therapies for CF
Commitments: 0.24 Calendar
Supporting Agency: NIH-NIDDK
Address:
9000 Rockville Pike
Bethesda, MD 20892
Contracting/Grants Officer:
Performance period: 6/1/2020-5/31/2021
Level of funding: Direct Cost
Project Goals: This is a proposal to continue our Cystic Fibrosis (CF) Research and Translation Core Center at the University of California, San Francisco and collaborating institutions. The focus of our Core Center remains the discovery and evaluation of novel small-molecule therapies for CF.
Role: Co-Investigator
Overlap: No scientific or budgetary overlap. If all the pending applications are funded, the PI will adjust his efforts accordingly to stay in compliance.

Title: Lung endothelial microRNA-1, a novel therapeutic target in ARDS
Commitments: 0.24 Calendar
Supporting Agency: Yale/NIH
Address:
New Haven
CT, 06520
Contracting/Grants Officer: Teresa Bohan
Performance period: 7/1/2022-6/30/2024
Level of funding: Direct Cost
Project Goals: The proposed studies in this NIH R01 application with Dr. Takyar will test a promising new therapeutic approach in our clinically relevant ex vivo perfused human lung preparation
Overlap: No scientific or budgetary overlap. If all the pending applications are funded, the PI will adjust his efforts accordingly to stay in compliance.

Title: Activation of plasmin(ogen)-S protein-host receptors cascade in COVID-19
Time Commitments: 0.24 calendar
Supporting Agency: UTHCT/NIH
Address:
9000 Rockville Pike

Bethesda, MD 20892
Contracting/Grants Officer:
Performance Period: 9/1/20-8/31/2021
Level of funding: Direct Cost
Project Goals: The results of these experiments will provide novel insights into mechanisms relevant for COVID-19 lung injury.
Overlap: *None*

Title: ENaC is an important target in SARS-Cov2-induced ARDS
Time Commitments: 0.24 calendar
Supporting Agency: NIH/Emory
Address:
9000 Rockville Pike
Bethesda, MD 20892
Contracting/Grants Officer:
Performance Period: 12/1/20-11/30/2025
Level of funding: Direct Cost
Project Goals: Provide human lung cells in primary culture as described and fixed tissue after SARS-Cov2 infection for microscopy.
Overlap: *None*

Title: ARREST RESPIRATORY FAILURE DUE TOPNEUMONIA (ARREST PNEUMONIA)
Time Commitments: 0.24 calendar
Supporting Agency: NIH/Stanford
Address:
9000 Rockville Pike
Bethesda, MD 20892
Contracting/Grants Officer:
Performance Period: 9/1/20-8/31/2024
Level of funding: Direct Cost
Project Goals: Dr. Joe Levitt at Stanford is leading a multicenter trial (ARREST) to test inhaled beta agonist / steroid versus placebo for actue respiratory failure NHLBI UH3
Overlap: *None*

Previous

Title: Study Chair for PETAL/ASTER
Commitments: 0.60 Calendar
Supporting Agency: MGH/NIH
Address:
55 Fruit St,
Boston MA 02114
Contracting/Grants Officer: Lynne A Benoit
Performance period: 6/1/2019-4/30/2020
Level of funding:
Project Goals: I will function as Chair for this clinical trial working on all aspects of protocol development, implementation and monitoring of the trial in conjuction with the Clinical Coordinating Center at Massachusetts General Hospital in Boston and the Lung Division at the NHLBI.**
Overlap: No scientific or budgetary overlap. If all the pending applications are funded, the PI will adjust his efforts accordingly to stay in compliance.

Title: *The GOLD STUDY: Goal of open lung ventilation in donors*
Time Commitments: *0.45 Calendar*
Supporting Agency: NIH/NHLBI, R01HL126176

Address:
NHLBI /VUMC
3319 West End Avenue, STE 100
Nashville TN 37203
***Contracting/Grants Officer**: Libby D. Salberg*
***Performance period:** 5/1/2016-5/31/2021*
Level of funding:
Project Goals: Dr. Matthay has 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 Vanderbilt.
***Overlap:** None*

Title: Mechanistic roles of Cytochrome P4501A enzymes in hyperoxic lung injury
***Time Commitments:** 0.45 Calendar*
***Supporting Agency:** NIH/NHLBI R01HL129794/ Baylor College of Medicine*
Address:
Baylor College of Medicine
One Baylor Plaza, BCM310
Houston, TX 77030-3411
***Contracting/Grants Officer:** Leanne B. Scott, Ph.D*
***Performance Period:** 04/01/2016-03/31/20*
Level of funding:
Project Goals: Mechanistic roles of cytochrome P4501A enzymes in hyperoxic lung injury
These analyses will specifically relate to the mouse studies with the metabolomics data and the planned proteomic studies.
***Specific Aims:** To study biomarkers as reliable indices of acute lung injury.*
***Overlap:** None*

Title: University of California, San Francisco (UCSF) CIRM Alpha Stem Cell Clinic
Time Commitments: 2.52 calendar
Supporting Agency: CIRM/CHORI
Address:
1999 Harrison Street, Suite 1650
Oakland, CA 94612
Contracting/Grants Officer: Michael Worden
Performance Period: 10/01/2017-09/30/2019
Level of funding:
Project Goals To address these gaps and expand clinical trial activity in cell therapies, the specific aims for an Alpha Stem Cell Clinic at UCSF at the above locations will be designed to accelerate the temple of pre-award planning, clinical trial activation, patient accrual and trial completion, expand access to these therapies by under-represented populations with disorders in the Alpha Stem Cell Network, and to establish a disease team approach that promotes participation in the CIRM Alpha Stem Cell Network trials
***Overlap:** None*

Title: Pulmonary Hypertension in ARDS study (To define the clinical and biological correlates of pulmonary hypertension and increased pulmonary dead space in patients with ARDS.)
***Time Commitments:** 1.2 calendar*
***Supporting Agency:** Bayer AG*
Address:
Bayer AG
Aprather Weg 18a
D-42113 Wuppertal
GDWRC/building WUP 431 2 223
***Contracting/Grants Officer:** Hubert Trübel*
***Performance Period:** 7/1/17-6/30/19*
Level of funding:

Project Goals: To determine the relationship of elevated pulmonary arterial pressures and elevated dead space to respiratory outcomes, 28 day mortality and biological markers of lung and systemic injury
Specific Aims: To determine incidence of pulmonary hypertension in ARDS patients and whether it identifies patients with a higher mortality along with measurement of pulmonary dead space and biologic markers of inflammation and lung injury.
Overlap: *None*

Title: Targeting Angiopoietin-2 in ARDS
Time Commitments: 0.21 calendar
Supporting Agency: *NHLBI/University of Pennsylvania (R01 HL137006)*
Address:
Office of Research Services
3451 Walnut St, 5th Floor Franklin Building
Philadelphia PA 19104-6205
Contracting/Grants Officer: *Amy Camilleri*
Performance Period: *2/1/18-2/28/18*
Level of funding:
Project Goals: The major goals are to test the role of angiopoietin-2 (ANG2) as a predictor of acute respiratory distress syndrome (ARDS) risk and evaluate early anti-ANG2 therapy to decrease lung leak in an ex vivo lung perfusion model of human disease.
Overlap: None

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:
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: *Resolution of Clinical Lung Injury*
Time Commitments: *0.12 calendar (NO COST EXTENSION)*
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: *04/01/2011-03/31/2018*
Level of funding:
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: *0.12 calendar (NO COST EXTENSTION)*
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: *09/01/2011-06/30/2018*
Level of funding:
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: 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:
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:
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:
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:
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:
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:
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:
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:
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:
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, HHSN2681100051*
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:
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*

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:
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: *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: *12/03/2013-06/02/2017*
Level of funding*:*
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: *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: *06/26/2012-07/31/2017*
Level of funding:
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: *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: *12/15/2011-11/30/2017*
Level of funding:
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: 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: *3/15/2016-1/15/18*
Level of funding:
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