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TITLE: Mesenchymal Stem Cells for Treatment of ARDS Following Trauma

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

CONTRACTING ORGANIZATION: University of California, San Francisco, CA

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8. PERFORMING ORGANIZATION REPORT NUMBER

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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 lim the severity and/or progression of lung injuries that lead to ARDS and death is an immediate clinical need in both military and civilia sectors. Experimental studies carried out in small and large animals have demonstrated that specialized cells called mesenchymal strom cells (MSC) can effectively reduce inflammation in multiple diseases including ARDS. The overall objective of this proposal is to carry ou a randomized, blinded, placebo-controlled, multicenter phase 2b trial to test the therapeutic potential of allogeneic bone-marrow derive MSC for treating ARDS. The specific aims of this project are: **Specific Aim 1**. To test the clinical efficacy of intravenously delivere allogeneic human MSC in patients with ARDS. **Specific Aim 2.** To test the mechanisms by which MSC reduce acute lung injury in patient with ARDS.

15. SUBJECT TERMS
None listed.

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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. In addition, with the start of the COVID-19 pandemic in February 2020 there was a substantial increase in the incidence of ARDS from this severe viral pneumonia from SARS-Co-V2 (Wick KD, McAuley D, Levitt JE, Beitler JR, Annane D, Riviello ED, Calfee CS, Matthay MA. Promises and challenges of personalized medicine to guide ARDS therapy. Crit Care, 2021; 25(1):404; PMID: 34814925).

2. KEYWORDS: Acute respiratory distress syndrome, pulmonary edema, trauma, pneumonia, sepsis, COVID-19

3. ACCOMPLISHMENTS:

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

In Year 5, our major goals were as follows:

1. Continue to recruit patients at all seven participating sites to reach the recruitment target of 120 patients.
2. Revise the study documents (e.g. Clinical Protocol with Protocol Amendment 4, Investigator Brochure, Case Report Form, Statistical Analysis Plan) to include COVID-19 specific information, additional secondary endpoints and data collection.

3. Submissions to the single IRB at VUMC, which mainly the following tasks: (1) Study annual renewal; (2) Submit protocol amendment 4 to collect additional COVID-19 information and related data before study close-out; (3) Submit the added or revised site-specific consent context documents for individual site.
4. Submit IND amendment and annual progress report to the FDA under IND 15331.
5. Submit study renewal and protocol amendment to the DoD HRPO to obtain the DoD approvals.
6. Submit No Cost extension application to the DoD for September 2022 to September 2023 with a spending plan.
7. Hold a six-month DSMB teleconference for safety review.
8. Hold monthly teleconference with the study investigators and study coordinators at all participating sites.
9. Retrospectively review medical records and complete the data entry for newly added COVID-19 information.
10. Continue to issue and respond to the data queries for all sites.
11. Continue to provide education and support for study conduct at all sites

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

Goal #1: Continue to recruit patients into the trial at 7 participating sites to reach the enrollment target of 120 patients - approaching

Currently all 7 sites are actively recruiting patients into the trial. As of October 4, 2022, we have enrolled a total of 119 patients into the trial and we are screening for these last patient for recruitment into the clinical trial. The enrollment numbers at individual participating sites are listed as below:

17 patients at UCSF,
40 patients at ZSFG,
15 patients at OHSU,
10 patients at UTHSCH,
11 patients at Vanderbilt University Medical Center
10 patients at UC Davis
16 patients at UW-Harborview Medical Center

Of the 119 patients, 101 patients have been COVID-19 positive. All 109 patients completed the study product infusion without serious adverse events related to the study product infusion.

Since the study initiation, there have been a total of 43 deaths - 31 deaths within 28 study days and 12 deaths over 28 study days and all were reported Dr. Taylor Thompson, the Research Monitor and the Chair of DSMB. None of these deaths were considered to be related to the study.

Goal #2: Revise the protocol to include COVID-19 specific information, additional secondary endpoints and data collection - completed

Since the COVID-19 pandemic, the vast majority of our enrolled patients were COVID-19 patients who developed ARDS. Therefore, during the past reporting year, we have amended the Clinical Protocol to include COVID-19 specific information, additional secondary endpoints and the related study procedures and data collection. The main motivation for this protocol amendment was to explicitly include the clinical and biologic variables relevant to COVID-19 included ARDS. We have also updated the related study documents for this Phase 2b trial listed as below:

Clinical Protocol:

We have revised the Clinical Protocol to include COVID-19 specific information, additional secondary endpoints, and related study procedures and data collection in April 2022 (Protocol No: UCSF-hMSC-ARDS-P1P2-14, dated April 19, 2022). The minor protocol changes include:

- Include COVID-19 information, as well as other secondary endpoints (respiratory, systematic illness, thromboembolic, biologic) and the related study procedures and data collection.
- Additional data analyses of primary and secondary endpoints by adjusting for SARS-CoV-2 infection.
- Add the new funding source (California Institute for Regenerative Medicine) to fund University of California Davis as an additional recruitment site.

Investigator Brochure:

We have updated the Investigator Brochure to reflect the changes in the Clinical Protocol. During the past reporting year, we have developed an updated version of Investigator Brochure: Version 14 (dated April 19, 2022, current version).

Informed Consent Form (ICF):

We use the Vanderbilt IRB as the single IRB (sIRB) for this Phase 2b trial. According to Vanderbilt IRB's guidelines, the consent forms at each site includes two parts: a main consent (Part 1), which is used for all seven sites; and a local consent context form (Part 2), which has site-specific language.

The main consent has no changes. The current version 1.5 is dated June 24, 2020. This main consent form has also been translated into Spanish and Russian, approved by the sIRB and is valid until 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 reporting year, we have made a 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 12, 2022.

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 April 28, 2022.

Goal #3: Submissions to single IRB at VUMC, which mainly the following tasks: (1) Renew the Phase 2b clinical trial; (2) Submit a protocol amendment to collect additional COVID-19 information, additional secondary endpoints and analyses; (3) Additional translated short forms for Harborview Medical Center; (4) Updated Bill of Rights for UCSF. – 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 single IRB at Vanderbilt University:

1. **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.

2. **IRB Amendment 19:** **Submission date:** 10/22/2021 **Approval date:** 10/23/2021

   Description: We submitted two non-English short forms (Vietnamese and Somali) for Harborview Medical Center. These short consent forms have been revised from the English short form provided by the Vanderbilt IRB.

3. **IRB Renewal:** **Submission date:** 01/25/2022 **Approval date:** 02/24/2022

   Description: We submitted the IRB renewal request to the sIRB at VUMC for all seven sites: UCSF, ZSFG, UTHSCH, Harborview, OHSU, VUMC and UCD. We also submitted the DSMB recommendation letter (dated 02/03/2022) to the sIRB in this renewal. The new IRB expiration date is February 23, 2023.

4. **IRB Amendment 20:** **Submission date:** 02/03/2022 **Approval date:** 02/09/2022

Description: UCSF IRB revised the Bill of Rights and translated into different languages, as well as translated/certified the existing English HIPPA forms. In this amendment, we submitted the revised Bill of Rights (English) and its five translated versions (serve as "short form"). We also submitted the E-consent forms for both UCSF and ZSFG (affiliated to UCSF) with the updated Bill of Rights and translated HIPPA forms.

5. **IRB Amendment 21:** **Submission date:** 05/12/2022 **Approval date:** 05/28/2022

   Description: We submitted the IRB amendment for the following changes: (1) updated the Clinical Protocol with Protocol Amendment 4, to include COVID-19 specific information, additional secondary endpoints and related study procedures and data collection; (2) updated the IRB application form to reflect the new changes in the Clinical Protocol; (3) updated the Investigator Brochure to reflect the minor protocol revision; (4) updated Statistical Analysis Plan to reflect the protocol changes; (6) updated Case Report Form.

Goal #4: Submit IND amendment and annual progress report to the FDA under IND 15331 – completed

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

1. **IND 15331 #0027:** **Submission date:** 03/16/2022

   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 #0028:** **Submission date:** 05/26/2022

   This IND amendment submission included the following tasks and updates:
   - Submission of the revised General Investigational Plan (dated 05/13/2022)
   - Submission of the amended Clinical Protocol (Version 14, dated 04/19/2022).
   - Submission of the revised Investigator Brochure (Version 14, dated 04/19/2022)
   - Submission of the updated Case Report Form (dated 05/12/2022)
   - Submission of the updated Statistical Analysis Plan (dated 04/28/2022)

Goal #5: 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 – All sites:** On March 3, 2022, 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 23, 2022.

2. **Protocol Amendment 4 – All sites**: The IRB amendment regarding the Clinical Protocol Amendment 4 was approved by the sIRB at VUMC on May 28, 2022. On June 8, 2022, 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 14, dated 04/19/2022) and Protocol Amendment 4 listing all proposed protocol changes;
   - Updated Investigator Brochure (Version 14, dated 04/19/2022);
   - Revised Case Report Form (dated 05/12/2022);
   - Updated Statistical Analysis Plan (dated 04/28/2022);

   The DSMB HRPO officer reviewed and approved this protocol amendment submission on August 2, 2022.

Goal #6: Submit No Cost Extension application to the DoD - completed

We submitted No Cost Extension (NCE) application to the DoD for September 15, 2022 to September 14, 2023 with a spending plan to complete the following Statement of Work tasks: (1) Follow up enrolled patients up to 6 months; (2) Clinical data analyses and biomarker measurements and analyses after patient enrollment completion. The DoD approved this application on September 11, 2022.

Goal #7: Hold 6-month DSMB teleconference for safety review - completed.

We submitted the materials to the DSMB for review on December 22, 2022, which included the safety report dated 12/22/2021 with unblinded (A vs B) data for 109 participants enrolled, as well the new death narratives and the protocol specified adverse event (participant 701, which was reported to the DoD in our 14th quarterly report and our annual progress report in 2021), and the subsequent material and revised death reports submitted in the interim were reviewed by the DSMB. The DSMB recommends that the study continue.

Goal #8: Monthly teleconference with the study investigators and study coordinators at all participating sites – in progress

We have regular one-hour monthly teleconferences with the study investigators, study coordinators and Stem Cell Lab personnel at all participating sites (second Wednesday 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 #9: Retrospectively review the medical charts and complete the data entries of newly added COVID-19 information – in progress

We have revised the Case Report Form to require COVID-19 information and the related clinical data from all enrolled patients. We reviewed changes to the CRF changes on our monthly teleconferences and via email communications. The CRCs at all sites have been conducting a retrospective review of medical records and data acquisition and data entries into our system.

Goal #10: Continue to issue and respond to the data queries at all sites – in progress

The data managers at Clinical Coordinating Center at UCSF have been sending data queries to each site and reviewing the revisions and responses to these queries. We have monitored and reported the query progress at our monthly teleconference.

Goal #11: Continue to provide education and support for study conduct at all sites – in progress

We have provided constant consultation by phone calls (especially to the PI, Dr. Matthay) and emails for any research related questions. 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 one more patient into the trial to reach the enrollment target of 120 patients
  2. Submit materials to the DSMB for 6-month safety review
  3. Retrospective review and data acquisition for newly added COVID-19 and related clinical data
  4. Continue to conduct data quality check and data query monitoring
  5. Continue to provide education and support for study conduct at all sites

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**

A. Protocol Amendment 4 (dated 04/19/2022) includes the following changes, all of which are considered minor revisions.

i. Include COVID-19 information in the Updated Clinical Protocol;
ii. Add additional secondary endpoints (respiratory, systemic illness, thromboembolic, biological);
iii. Conduct additional primary and secondary endpoints analyses adjusting for SARS-CoV-2 infection;
iv. Update study procedures to reflect the amended protocol, including concomitant therapies, radiographic assessment of lung edema (RALE) score;
v. Expand clinical data collection related to COVID-19 information
vi. Add California Institute for Regenerative Medicine for funding University of California Davis as an additional enrollment site.

- **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.

B. 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.

C. 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: 5.79
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: 0.93
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: 2.0
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: 0.39
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: 1.08
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: 1.05
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: 0.6
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: 09.36
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: 4.34

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: 0.42
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: 09.15
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: 8.36
Contribution to Project: Worked on the MSC biology studies

Deanna Lee
Project Role: Clinical Research Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 2.92
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

Byron Miyazawa
Project Role: Clinical Research Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 2.92
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

Erwin Ni
Project Role: Clinical Research Coordinator
Research Identifier: 0000-0003-3039-8155
Nearest person month worked: 6.01
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.

D. SPECIAL REPORTING REQUIREMENTS:

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

E. **APPENDICES:**

1. **DoD (STAT) trial DSMB recommendation (dated February 3, 2022)**

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

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Division of Pulmonary and Critical Care Medicine,
Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

DoD (STAT) Trial DSMB Recommendations
Feb 3, 2022

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

Dear Dr. Matthay,

Materials submitted to the DSMB for review on December 22, 2022, including the safety report dated 12/22/2021 with unblinded (A vs B) data for 109 participants enrolled, as well the new death narratives and the protocol specified adverse event (participant 701) and the subsequent material and revised death reports submitted in the interim were reviewed by the DSMB.

The DSMB recommends that the study continue.

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: *9/15/2017-9/14/2023 (NCE 2)*
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: 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*: 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: *7/1/20-6/30/2023 NCE*
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: 10/1/2019-10/31/2022
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:** 0.24 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

***Title**: Novel exosomal niches for alveolar stem cell-based repair of septic lungs*
***Time Commitments:** 0.24 Calendar*
Supporting Agency: University of Texas Health Science Center at Tyler / NIH R01HL134828
Address:
11937 U.S. Highway 271
Tyler, TX 75708-3154
***Contracting/Grants Officer**:*
***Performance period:** 5/15/2022-4/30/20206*
***Level of funding:** Direct Cost*
Project Goals:
Role: Co-Investigator
Overlap: None

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: 8/1/2020-5/31/2023
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.
Role: PI
Overlap: No scientific or budgetary overlap.

Title: ARREST RESPIRATORY FAILURE DUE TOPNEUMONIA (ARREST PNEUMONIA)
Time Commitments: 0.12 calendar
Supporting Agency: NIH/Stanford
Address:

9000 Rockville Pike
Bethesda, MD 20892
Contracting/Grants Officer:
Performance Period: 9/1/19-8/31/2024
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
Role: PI
Overlap: *None*

Title: International Coordinating Center for ACTIV-3 Trail Initiative
Time Commitments: 0.12 calendar
Supporting Agency: NIH/Massachusetts General Hospital
Address:
NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Contracting/Grants Officer:
Performance Period: 6/10202-5/31/2022 pending NCE
Level of funding Direct Cost
Project Goals: Dr. Matthay will serve as Protocol Team Member (Study Chair) of the International Coordinating Center for ACTIV-3 Trial Initiative protocols
Role: PI
Overlap: *None*

Title: I-Spy Covid Trial Biomarker Expansion and Trial Site
Time Commitments: 0.60 calendar
Supporting Agency: Quantum Leap Healthcare Collaborative
Address:
3450 California St.
San Francisco, CA 94143
Contracting/Grants Officer:
Performance Period: 1/1/2021-12/31/2022
Level of funding: Total Cost
Project Goals: I-Spy 2 Trail (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis): An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy
Role: Co-PI
Overlap: *None*

Title: Molecular Profiling of ARDS Edema Fluid: a Window to an Injured Leg
Time Commitments: 0.12 calendar
Supporting Agency: NIH / Stanford R01HL152083
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer:
Performance Period: 08/1/2020-5/31/2025
Level of funding: Direct cost
Project Goals: We will collect clinical and biologic samples from 20 patients with ARDS at UCSF in order to support the primary purpose of Dr. Angela Rogers' R01 application to study the mechanisms of Acute Lung Injury in ARDS.
Role: PI
Overlap: *None*

Title: Mesenchymal modulation of epithelial metaplasia in lung fibrosis
Time Commitments: 0.12 calendar
Supporting Agency: NIH R01 HL155622
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer: Anthony Agresti
Performance Period: 2/1/2021-12/31/2024
Level of funding: Direct cost
Project Goals: The proposal aims to address how the mesenchymal compartment of the progenitor niche modifies epithelial plasticity in fibrotic repair; and outlines a potential pre-clinical pipelines to identify compounds that can target epithelial metaplasia in lung fibrosis
Role: Co-PI
Overlap: *None*

Title: A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitals Aduolts with COVID-19.
Time Commitments: 0.12 calendar
Supporting Agency: NIH / NYU Langone Health System/ Massachusetts General Hospital
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer: Anthony Carna
Performance Period: 6/1/20-12/31/222 (NCE)
Level of funding: Direct cost
Project Goals: This is a randomized, open lable, adaptive platform trial to compare the effectiveness of antithrombotic strategies for prevention of adverse outcomes in COVID-19 positive inpatients
Role: PI
Overlap: *None*

Title: CCC for NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Network (ASTER Protocol) Chair
Time Commitments: 0.12 calendar
Supporting Agency: NIH / Massachusetts General Hospital
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer:
Performance Period: 8/1/21-10/31/22
Level of funding: Direct cost
Project Goals: The Protocol, "Acetaminophen and Ascorbate in Sepsis; Targeted Therapy to Enhance Recovery (ASTER)" is incorporated to this Agreement by reference and sent under separate cover to Site and Site Investigator.
Role: PI
Overlap: *None*

Title: International Coordinating Center for ACTIV-3 Trial Initiative VACTICO Pathway
Time Commitments: 0.12 calendar
Supporting Agency: NIH / Massachusetts General Hospital
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer:

Performance Period: 8/1/2021-5/31/2023
Level of funding Direct cost
Project Goals: The Protocol, "SARS-CoV-2 Vaccination strategies in previously hospitalized and recovered COVID-19 patients (VACTICO INSIGHT 016)
Role: PI
Overlap: *None*

Pending

Title: Effects of smoking and vaping on SARS-CoV-2 infection in organoid and whole lung models.
Commitments: 1.20 Calendar
Supporting Agency: NIH-CSR P0554839
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer:
Performance period: 04/01/2022-03/31/2027
Level of funding: Direct Cost
Project Goals: Study the pathogenesis of smoking on SARS-CoV-2 infection
Role: PI
Overlap: No scientific or budgetary overlap.

Title: Determinants and Significance of Respiratory Drive in Acute Respiratory Failure
Commitments: 0.24 Calendar
Supporting Agency: NIH CSR / Columbia University of Medical Center P0558224
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer:
Performance period: 07/1/2022-6/30/2027
Level of funding: Direct Cost
Project Goals:
Role: PI
Overlap: No scientific or budgetary overlap.

Previous

Title: International Coordinating Center for ACTIV-3 Trial Initiative VACTICO Pathway
Time Commitments: No PI Effort
Supporting Agency: NIH / Massachusetts General Hospital
Address:
NHLBI Health Information Center
P.O. Box 30105
Contracting/Grants Officer: Lynne A Benoit
Performance Period: 8/1/2021-5/31/20222
Level of funding: Direct cost
Project Goals: The Protocl, "SARS-CoV-2 vaccination strategies in previously hospitalized and revoerd COVID-19 patients (VATICO INSIGHT 016)
Overlap: *None*

Title: Testing Disulfiram and Combinations for Acute Lung Injury from Pneumonia in Mice
Commitments: 0.12 Calendar
Supporting Agency: Spring Discovery Inc
Address:
1121 Industrial Road, Suite 500
San Carlos, CA 94070
Contracting/Grants Officer: Matt Donne
Performance period: 2/1/2021-7/30/2021
Level of funding: Direct Cost
Project Goals: Pilot Study- Spring discovery Pneumococcal ARDS Mouse study
Overlap: No scientific or budgetary overlap.

Title: ENaC-α mediates lung fluid clearance and capillary barrier function in pneumonia
Commitments: 0.12 Calendar
Supporting Agency: Augusta University/ NIH
Address:
1120 15th Street
Augusta, GA 30912
Contracting/Grants Officer: Sandy Ferguson
Performance period: 7/1/2020-6/30/2022
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.
Role: PI
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: 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: 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: *9/1/2017-5/14/2022*
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: 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: 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: *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: *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