

Award Number: W81XWH-13-2-0024

TITLE: Stem Cell Therapy To Improve Burn Wound Healing

PRINCIPAL INVESTIGATOR: Carl Schulman, MD, PhD, MSPH, FACS

CONTRACTING ORGANIZATION: University Of Miami  
CORAL GABLES, FL 33146

REPORT DATE: May 2019

TYPE OF REPORT: Final Report

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

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

**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 information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

|   |                         |                                |                                   |   |   |
|---|-------------------------|--------------------------------|-----------------------------------|---|---|
| <b>1. REPORT DATE</b><br>May-2019   |                         | <b>2. REPORT TYPE</b><br>Final |                                   | <b>3. DATES COVERED</b><br>15-Feb-2013 to 14-Feb-2019 |   |
| <b>4. TITLE AND SUBTITLE</b><br>Stem Cell Therapy To Improve Burn Wound Healing   |                         |                                |                                   | <b>5a. CONTRACT NUMBER</b>                            |   |
|   |                         |                                |                                   | <b>5b. GRANT NUMBER</b><br>W81XWH-13-2-0024           |   |
|   |                         |                                |                                   | <b>5c. PROGRAM ELEMENT NUMBER</b>                     |   |
| <b>6. AUTHOR(S)</b><br>Carl Schulman, MD, PhD, MSPH, FACS<br><br>E-Mail: CSchulman@med.miami.edu  |                         |                                |                                   | <b>5d. PROJECT NUMBER</b>                             |   |
|   |                         |                                |                                   | <b>5e. TASK NUMBER</b>                                |   |
|   |                         |                                |                                   | <b>5f. WORK UNIT NUMBER</b>                           |   |
| <b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b><br><br>University of Miami Miller School of Medicine<br>Ryder Trauma Center<br>1800 NW 10 <sup>th</sup> Avenue, Suite 221<br>Miami, FL, 33136   |                         |                                |                                   | <b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>       |   |
| <b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b><br>U.S. Army Medical Research and Materiel Command<br>Fort Detrick, Maryland 21702-5012  |                         |                                |                                   | <b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>               |   |
|   |                         |                                |                                   | <b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>         |   |
| <b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b><br>Approved for Public Release; Distribution Unlimited   |                         |                                |                                   |   |   |
| <b>13. SUPPLEMENTARY NOTES</b>  |                         |                                |                                   |   |   |
| <b>14. ABSTRACT</b><br>Thermal injuries are a significant source of morbidity in times of war, constituting 5% to 20% of all injuries and 4% of all deaths. Although these are usually not life threatening, they cause significant morbidity to the patient and disruption of a deployed military unit. Hypertrophic scarring occurs frequently in operative (grafted) and non-operative burn wounds and can lead to the formation of scar contractures. Contractures represent a great source of morbidity to burn patients. Scar contracture rates have not evolved with improvements of burn care despite the use of treatments designed to mitigate the effects of hypertrophic scarring including scar massage, topical treatments, steroid injections, and compression garments. Mesenchymal stem cells (MSC's) have been used in a variety of clinical applications to repair and regenerate damaged tissue. Previous work by our group has demonstrated the safety and efficacy of delivering bone marrow cells including MSC's to chronic wounds with significant improvement in healing and scarring. Application of mesenchymal stem cell (MSC) therapy to severe burn wounds represents the opportunity for improved outcomes where alternate therapies are limited and often ineffective. |                         |                                |                                   |   |   |
| <b>15. SUBJECT TERMS</b><br>wound healing, stem cell therapy, mesenchymal stem cells, MSC   |                         |                                |                                   |   |   |
| <b>16. SECURITY CLASSIFICATION OF:</b>  |                         |                                | <b>17. LIMITATION OF ABSTRACT</b> | <b>18. NUMBER OF PAGES</b>                            | <b>19a. NAME OF RESPONSIBLE PERSON</b><br>USAMRMC |
| <b>a. REPORT</b><br>U   | <b>b. ABSTRACT</b><br>U | <b>c. THIS PAGE</b><br>U       |                                   |   | <b>19b. TELEPHONE NUMBER</b> (include area code)  |
|   |                         |                                | UU                                | 13  |   |

**Table of Contents**

INTRODUCTION.....4

BODY.....4

OVERALL PROGRESS.....4-11

PROBLEM AREAS.....11

CONCLUSION.....12

UPCOMING PERFORMANCE PERIOD.....12

ADMINISTRATIVE COMMENTS.....12

## **INTRODUCTION**

The purpose of the research effort is to evaluate the safety and efficacy of mesenchymal stem cells in the treatment of burn wounds. The scope of the research is a Phase I and II clinical trial.

## **KEYWORDS**

wound healing, stem cell therapy, mesenchymal stem cells, MSC

## **ACCOMPLISHMENTS:**

- What were the major goals of the project?
  - Major goal was to establish the safety of MSC application for second degree burns.
- What was accomplished under these goals?
  - The enrollment of patients in 3 escalating dose groups confirmed the safety of MSC application for second degree burns.
- How were the results disseminated to communities of interest?
  - Publications are in progress.
- What do you plan to do during the next reporting period to accomplish the goals?
  - Nothing to report

## **IMPACT:**

- What was the impact on the development of the principal discipline(s) of the project?
  - Further affirms the potential for allogeneic mesenchymal stem cell therapy in the treatment of burns.
- 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.

## **OVERALL PROGRESS**

### **A. Personnel:**

- Added Naiem Issa, Divya Aickara, and Luis Rodriguez-Menocal
- Removed Ambar Candanedo

### **B. Approvals:**

UM IRB approvals since last report:

#### **1. Continuing Review 2018 and Modification # 23 MODCR00001564 sent to UM IRB on 16 Mar, 2018**

- a. Documents submitted with the report:
  - SAE Initial Report R027-F-A
  - Deviation Log 2017-2018
  - DSMB letters and report Mar 2018
  - DSMB letters and report Sep 2017
  - Continuing review 2018 Grant Progress report
  - Protocol 20120925 14Nov 2017 FDA Approved
  - 20120925 Protocol Changes- Summary 23Mar2018
- b. IRB Approval 16 Apr 2018, IRB Approval letter sent on 17 Apr 2018
- c. Continuing Review 2018 MODCR00001564 approved by UM IRB, sent to the Department of Defense.

#### **2. Modification # 24 sent on 15 Aug, 2018**

- a. Documents submitted with the report:

- Notification letters for subjects
  - To remind the subject to schedule a study visit.
  - To inform noncompliant subjects that their study participation will be discontinued.
- b. To add Naiem Issa as a study team member
- c. IRB Approval 25 Aug 2018, IRB Approval letter sent on 27 Apr 2017

**3. Modification # 25 sent on 07 Sep, 2018**

- a. To add Divya Aickara as a study team member.
- b. IRB Approval 11 Sep 2018, IRB Approval letter sent on 11 Sep, 2018

**4. Modification # 26 no report, error, discarded**

**5. Modification # 27 sent on 18 Oct, 2018**

- a. Documents submitted with the report:
  - JHS CTO Application Form 2012
  - JHS CTO Application Form 2014
  - JHS Study Calendar Signed 10-27-15
  - CTRS Service Request Form
  - UMH Application Form-UMH Letter
  - Pathology Protocol Questionnaire
- b. To add Luis Rodriguez-Menocal as a study team member
- c. IRB Approval 11 Oct 2018, IRB Approval letter sent on 11 Oct 2018

**6. Modification # 28 sent on 3 Dec, 2018**

- a. To remove Ambar Candanedo from the study team.
- b. IRB Approval 7 Dec 2018, IRB Approval letter sent on 7 Dec 2018

**7. New Reportable Information – Study Pause in Enrollment on 19 Dec 2018**

- Due to recent media coverage of other institutions of higher learning voluntarily pausing their stem cell clinical trials to review practices and procedures in translational stem cell therapy, the University of Miami has decided to proactively pause enrollment and study treatment to all Mesenchymal Stem Cell (MSC) trials while a review is conducted

**8. New Reportable Information – Update to Study Pause in Enrollment on 26 Feb 2019**

- This study paused enrollment for new subjects on 12/18/2018. The NHLBI Data Safety and Monitoring Board reviewed the scientific literature and review of detailed investigator reports regarding the multi-center CONCERT-HF trial. This included a site visit to review cell production at ISCI. The NHLBI “concluded that the scientific basis and rationale for the CONCERT-HF trial remain sound, that the cell-based products met the criteria for clinical use, and that there were no new concerns related to participant safety. Based on the NIH review, we requested that the pause be lifted to reopen the clinical trial for enrollment of new subjects if needed.

**9. Continuing Review 2019 CR00010387 sent to UM IRB on 14 Mar, 2019**

- a. Documents submitted with the report:
  - Grant Progress Report (Enrollment Summary and Overall Progress)
- b. IRB Approval 10 Mar 2019, IRB approval letter send to DOD 01 Apr 2019

**C. Donors:**

No changes.

- Screened: 2
- Screen failed: 1
- Enrolled: 1

#### **D. Patients-Recipients:**

- Screened: 29
- Screen failure: 12
- Withdraw consent: 3
- Enrolled: 14
  
- Recipient #R001:
  - Screening visit (visit 1) completed on 8 Oct 2014.
  - First MSCs application (visit 2) on 14 Oct 2014.
  - This subject was not eligible for a second MSCs application because the wound was completely healed.
  - Patient completed his participation in the study. No adverse events reported.
  
- Recipient#R002:
  - Patient was a screen failure. No adverse events reported.
  
- Recipient #R003:
  - Screening visit (visit 1) completed on 15 Jan 2015.
  - First MSCs application (visit 2) on 20 Jan 2015.
  - This subject was not eligible for a second MSCs application because the wound was completely healed.
  - A serious adverse event was reported by the subject on 07 Apr, 2015. The patient has complained about gastrointestinal symptoms; this event is unlikely related to the study. Patient received a referral to GI.
  - Antral ulceration biopsy reported Gastric Cancer. Patient was successfully treated for Gastric Cancer. Final Adverse event report completed by Dr. Schulman.
  - Final visit completed on 12 Jul 2016. No other adverse events reported.
  
- Recipient #R004:
  - This patient did not show up on 08 Apr 2015 (Visit 3). We have been unable to contact this patient by phone. We sent two certified letters.
  - No adverse events reported.
  - Patient lost to follow up.
  
- Recipient #R005:
  - Patient was a screen failure. No adverse events reported.
  
- Recipient #R006:
  - Informed consent forms signed on 9 Oct 2015
  - Visit 1 screening on 9 Oct 2015
  - Visit 2 completed on 13 Oct 2015, first stem cells application.
  - Visit 4 completed on 23 Oct 2015, second stem cells application.
  - Patient completed his participation in the study on 17 Jan 2017. No adverse events reported.
  
- Recipient #R007:
  - Informed consent forms signed on 17 Nov 2015
  - Patient did not return to clinic.
  
- Recipient #R008:
  - Patient was a screen failure. No adverse events reported.
  
- Recipient #R009:
  - Patient withdrew from study. No adverse events reported.

- Recipient #R010:
  - Informed consent forms signed on 15 Jan 2016
  - Visit 1 screening on 15 Jan 2016
  - Visit 2 completed on 20 Jan 2016, first stem cells application.
  - Visit 4 completed on 1 Feb 2016, second stem cells application.
  - Adverse events reported:
    - Left upper extremity weakness: Severity Mild. Unrelated to study treatment. No actions taken with study treatment. Continuing at final visit.
    - Persistent Hypertension: Severity Mild. Unrelated to study treatment. No actions taken with study treatment. Resolved on 10 Jan 2017
  - Patient completed his participation in the study on 15 Feb 2017. No other adverse events reported.
  
- Recipient #R011:
  - Informed consent forms signed on 05 Feb 2016
  - Visit 1 screening on 05 Feb 2016
  - Visit 2 completed on 12 Feb 2016, first stem cells application.
  - Visit 4 completed on 23 Feb 2016, second stem cells application.
  - Patient completed his participation in the study on 01 Feb 2017. No adverse events reported.
  
- Recipient #R012:
  - Informed consent forms signed on 05 Apr 2016
  - Visit 1 screening on 05 Apr 2016
  - Visit 2 completed on 08 Apr 2016, first stem cells application.
  - Visit 4 completed on 20 Apr 2016, second stem cells application.
  - Adverse events reported:
    - New burn left forearm: Severity Mild. Unrelated to study treatment. No actions taken with study treatment. Resolved on 02 May 2017
  - Patient completed his participation in the study on 02 May 2017. No other adverse events reported.
  
- Recipient #R013:
  - Informed consent forms signed on 06 Sep, 2016
  - Visit 1 screening on 06 Sep, 2016
  - Visit 2 completed on 09 Sep 2016, first stem cells application.
  - This subject was not eligible for a second MSCs application.
  - Adverse events reported:
    - PTSD: Severity Mild. Unrelated to study treatment. No actions taken with study treatment.
    - Cataract: Severity Moderate. Unrelated to study treatment. No actions taken with study treatment.
    - Sinus pressure: Severity Mild. Unrelated to study treatment. No actions taken with study treatment..
    - Tinnitus: Severity Moderate. Unrelated to study treatment. No actions taken with study treatment.
    - Hearing loss in right ear: Severity Mild. Unrelated to study treatment. No actions taken with study treatment.
    - Post-traumatic nasal obstruction with nasal fracture malunion and nasal airway obstruction, with septal deviation. Severity Severe. Unrelated to study treatment. No actions taken with study treatment. Outcome: Recovering/ Resolving.
    - Patient completed his participation in the study on 03 May 2017. No other adverse events reported.
  
- Recipient #R014:
  - Patient was a screen failure due to abnormal labs. No adverse events reported.
  
- Recipient #R015:
  - Informed consent forms signed on 13 Jan 2017
  - Visit 1 screening completed on 17 Jan, 2017

- Visit 2 completed on 19 Jan 2017, first stem cells application.
  - This subject was not eligible for a second MSCs application.
  - Patient completed his participation in the study on 08 Feb 2018. No adverse events reported.
- Recipient #R016:
    - Informed consent forms signed on 18 Jan 2017
    - Visit 1 screening completed on 19 Jan, 2017
    - Visit 2 completed on 20 Jan 2017, first stem cells application.
    - This subject was not eligible for a second MSCs application.
    - Patient completed his participation in the study on 24 Jan 2018. No adverse events reported.
- Recipient #R017:
    - Patient was a screen failure due to abnormal labs. No adverse events reported.
- Recipient #R018:
    - Patient was a screen failure due to abnormal labs. No adverse events reported.
- Recipient #R019:
    - Patient was a screen failure due to abnormal labs. No adverse events reported.
- Recipient #R020:
    - Informed consent forms signed on 13 Mar 2017
    - Visit 1 screening completed on 13 Jan, 2017
    - Visit 2 completed on 15 Mar 2017, first stem cells application.
    - This subject was not eligible for a second MSCs application.
    - Patient completed his participation in the study on 27 Apr 2018. No adverse events reported.
- Recipient #R021:
    - Patient was a screen failure due to an autoimmune disease. No adverse events reported.
- Recipient #R022:
    - Patient was a screen failure due to abnormal labs. No adverse events reported.
- Recipient #R023:
    - Informed consent forms signed on 18 Aug 2017
    - Visit 1 screening completed on 21 Aug 2017
    - Visit 2 completed on 23 Aug 2017, first stem cells application.
    - This subject was eligible for a second MSCs application. The cells were applied on 05 Sep, 2017
    - Patient completed his participation in the study 1 Mar 2018. No adverse events reported.
- Recipient #R024:
    - Patient was a screen failure due to abnormal labs and history of malignancy. No adverse events reported.
- Recipient #R025:
    - Patient was a screen failure due to abnormal labs. No adverse events reported.
- Recipient #R026:
    - Patient was a screen failure due to abnormal labs. No adverse events reported.
- Recipient #R027
    - Informed consent forms signed on 22 Feb 2018

- Visit 1 screening completed on 23 Feb 2018
  - Visit 2 completed on 27 Feb 2018 first stem cells application.
  - This subject was eligible for a second MSCs application. The cells were applied on 12 Mar 2018.
  - Excision and auto grafting to the right thigh and leg on 16 Mar 2018
  - Serious adverse event was reported on 16 Mar 2018.
    - Post-op bleeding: Severity- severe. Unrelated to the study. No actions taken with study treatment. Recovered/Resolved.
  - Adverse events reported:
    - Wound bleeding: Severity Mild. Unrelated to study treatment. No actions taken with study treatment. Recovered/Resolved.
    - Urinary Tract Infection: Severity Mild. Unrelated to study treatment. No actions taken with study treatment. Recovered/Resolved.
  - Patient completed participation in the study on 5 Mar 2019. No other adverse events reported.
- Recipient #R028
    - Informed consent forms signed on 01 May 2018
    - Visit 1 screening completed on 01 May 2018
    - Visit 2 completed on 03 May 2018 first stem cells application.
    - This subject was eligible for a second MSCs application. The cells were applied on 14 May 2018.
    - Adverse events reported:
      - Rash: Severity Mild. Unlikely to be related to study treatment. No actions taken with study treatment. Recovered/ Resolved.
      - Worsening Rash: Severity Moderate. Unlikely to be related to study treatment. No actions taken with study treatment. Recovered/Resolved.
    - Patient completed participation in the study. No other adverse events reported.
  - Recipient #R029
    - Informed consent forms signed on 14 Sep 2018
    - Patient withdrew from study 17 Sep 2018. No adverse events reported.

**E. Research Monitor:** Clinical Research Operations & Regulatory Support (CRORS), University of Miami, has been providing support with the following areas:

- Good clinical practice
- Good documentation practice
- Informed consents
- Responsibilities for IND/IDE holders
- Investigational product
- Regulatory binder/trial master file
- Protocol compliance
- Assistance with the Audit process

Monitor visits:

- February 26, 27, and 28, 2018
- May 29 and 30, 2018
- August 21 and 22, 2018
- December 04 and 05, 2018
- March 19 and 20, 2019

**F. Sponsor's Scientific Summary:**

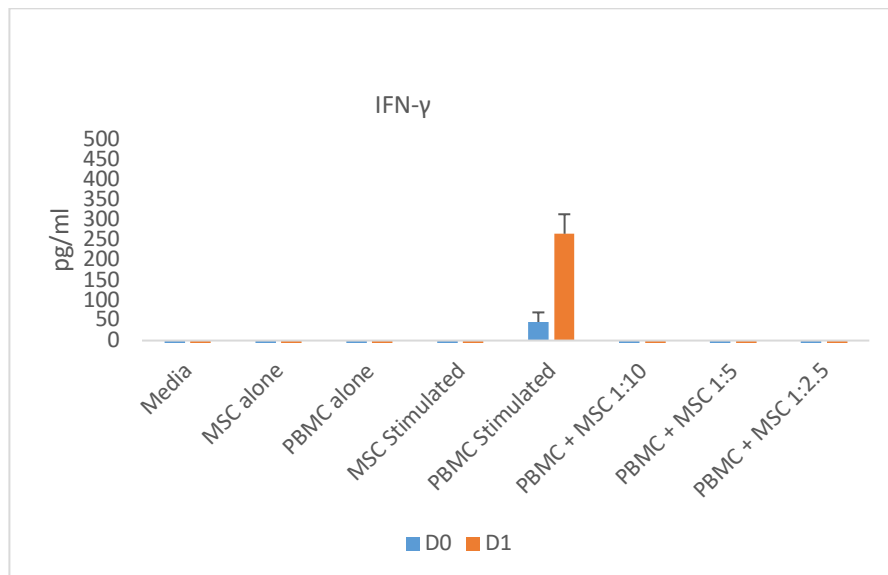
We concluded enrollment and follow up visits.

All patients (at all doses) treated to date that have completed cytokine analysis of mixed MSCs and Pre or Post treatment PBMCs have not demonstrated any significant elevations in IL10, IFN- $\gamma$  and TNF- $\alpha$  levels in of mixed MSC/PBMC reactions at all ratios. These findings support the immune privileged/immune suppressive effects of administered allogeneic MSCs with the lack of host immune response to these cells in burn patients. This should also be taken into consideration with clinical observations of improvement in healing without significant related adverse events in all patients at all dose levels. We observed varying baseline levels of cytokines prior to treatment which again support a disparity in immune response to burns in second degree burn patients. We have also noted that the ability to chemically stimulate patient PBMC (alone) to produce IFN- $\gamma$  and TNF- $\alpha$  returns after treatment with MSC. This has been noted in some patients (Figures A, B, and C). These findings suggest that MSC treatment induces a restoration of immune function following burn injury. The ability to stimulate IL10 however remains limited and may suggest the inability of host PBMC to adequately suppress the inflammatory state present in burn wounds.

As previously reported, we have also evaluated Extracellular Vesicles (EVs) released into the saline fluid where donor MSCs are placed for delivery to patients. Samples of MSC administered to patients demonstrate the presence of ample numbers of EVs in a wide distribution of particle sizes. We believe these EVs may be key mediators of the clinical response we have observed in patients.

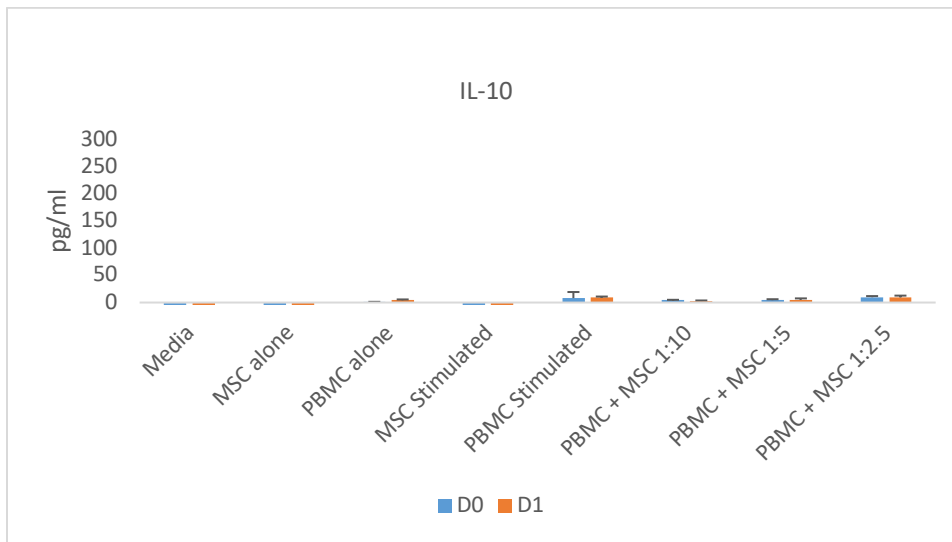
A skin biopsy sample was obtained from a subject 10 months after receiving one administration of cells at the second dose level. The biopsy revealed normal epithelialization with dermal remodeling. Reticular dermal elastic fibers with normal morphology were noted indicative of tissue regeneration. Special stains to further evaluate dermal structures are still being performed.

Figure A



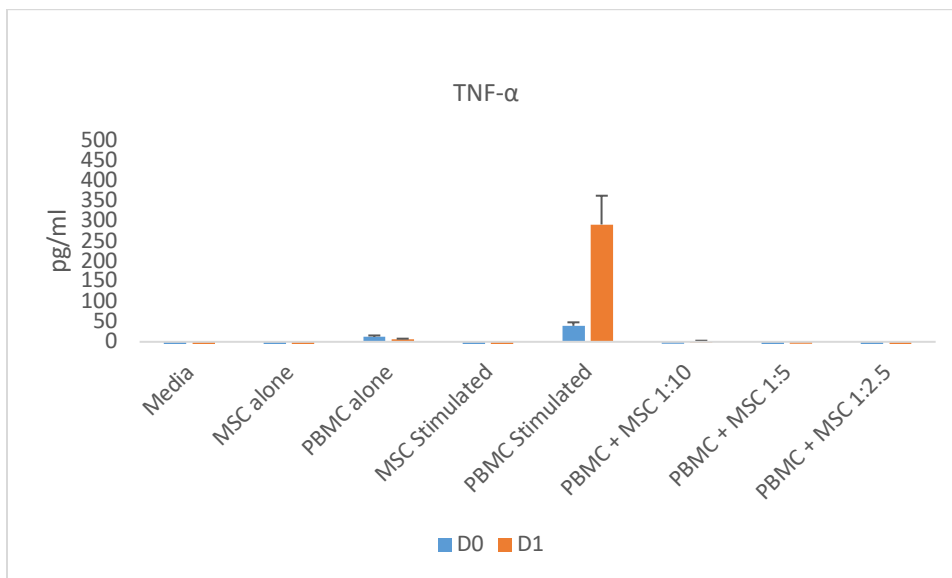
**Figure A: IFN-  $\gamma$  ELISA Assay.** All mixture ratios of PBMC and donor MSCs are non-reactive. PBMC stimulated is the positive control. (D0 = Blood sample taken at screening, prior to administration of donor MSCs; D1 = Blood sample taken after one week after cell application of donor MSCs.)

Figure B



**Figure B: IL-10 ELISA Assay.** Small, non-significant increase in mixture ratios of PBMC and donor MSCs PBMC stimulated is the positive control. IL-10 in stimulated PBMC is variable among patients. PBMC alone did not produce appreciable levels of IL-10. (D0 = Blood sample taken at screening, prior to administration of donor MSCs; D1 = Blood sample taken after one week after cell application of donor MSCs.)

Figure C



**Figure C: TNF- α ELISA Assay.** All mixture ratios of PBMC and donor MSCs are non-reactive. PBMC stimulated is the positive control. PBMC alone did not produce appreciable levels of TNF- α. (D0 = Blood sample taken at screening, prior to administration of donor MSCs; D1 = Blood sample taken after one week after cell application of donor MSCs.)

**PROBLEM AREAS**

- The enrollment for the study is closed.

## **CONCLUSION**

- See Scientific Summary

## **UPCOMING PERFORMANCE PERIOD**

- None. This is the final report

## **ADMINISTRATIVE COMMENTS**

- Quad Chart updated

## **PRODUCTS:** Nothing to report

- Publications, conference papers, and presentations
  - Currently pending publication.
- Technologies or techniques
  - Nothing to report
- Inventions, patent applications, and/or licenses
  - Nothing to report
- Other Products
  - Nothing to report

# Stem Cell Therapy To Improve Burn Wound Healing

Insert ERMS/Log Number and Task Title Here

W81XWH-13-2-0024



PI: Carl Schulman

Org: University of Miami

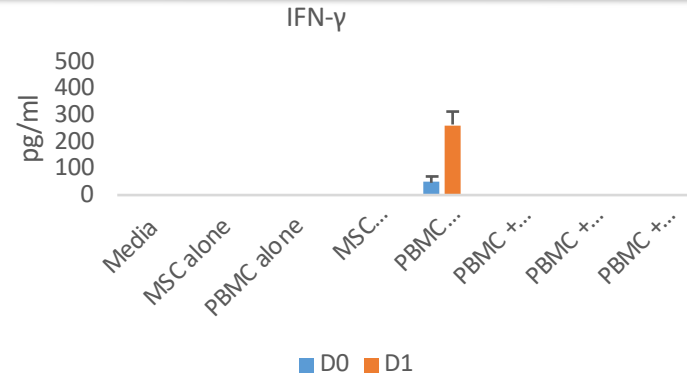
Award Amount: \$3,060,000

## Study/Product Aim(s)

- Perform Phase 1 Trial of Allogeneic MSCs in Burns
- Perform Phase 2 Trial of Allogeneic MSCs in Burns
- Collect Tissue Repository for Biomarker Evaluation

## Approach

Free text.



Accomplishments: All mixture ratios of PBMC and donor MSCs are non-reactive. This indicates safety of the MSC cell application.

## Timeline and Cost

| Activities   | CY | 14           | 15            | 16            | 17           |
|--|----|--------------|---------------|---------------|--------------|
| Obtain IRB approval and start donor recruitment,; Hire essential personnel |    | █            |               |               |              |
| Obtain donor MSCs and apply to patients                                    |    |              | █             |               |              |
| Enroll 80 patients for randomized trial, follow for 12 months              |    |              |               |               | █            |
| Collect samples for repository   |    |              |               | █             |              |
| <b>Estimated Budget (\$K)</b>  |    | <b>\$230</b> | <b>\$1200</b> | <b>\$1300</b> | <b>\$330</b> |

Updated: 05/15/2019

## Goals/Milestones

### CY13 Goal – Phase 1 Trial

- Obtain UM and DOD IRB approval, hire essential personnel

### CY14 Goals – Phase 1 and Phase 2 Trial

- Obtain donor MSCs and apply MSCs to patients. Maintain cells ready for application
- Start screen and Recruit 20 patients for safety/dose studies

### CY15 Goal – Continue Phase 1 and, Start Tissue Repository

- Continue donors recruitment, screening and Bone Marrow Aspiration as needed.
- Continue patients screening and enrollment.

- Collect blood and tissue samples to perform functional studies

### CY16 Goal – Continue phase 1 Trial and Collect Tissue Repository

- Continue donors recruitment, screening and Bone Marrow Aspiration as needed.
- Continue patients screening and enrollment.

- Collect blood and tissue samples to perform functional studies

### CY17 Goal – Continue phase 1 Trial, Start phase 2 trial and Collect Tissue Repository

- Continue donors recruitment, screening and Bone Marrow Aspiration as needed.
- Complete the screening and enrollment of 20 patients for safety/dose studies

- Collect blood and tissue samples to perform functional studies

### CY18 Goal – Complete phase 1 Trial, Start phase 2 trial and Collect Tissue Repository

- X Continue donors recruitment, screening and Bone Marrow Aspiration as needed.

- X Complete the screening and enrollment of 20 patients for safety/dose studies

- X Start the screening and enrollment of 80 patients in randomized trial

- X Collect blood and tissue samples to perform functional studies

- Follow patients for at least 6 months after the last MSCs application

## Comments/Challenges/Issues/Concerns

- Patients-Recipients: Screened: 29; Screen failure:12;Withdraw consent: 3;Enrolled: 14

## Budget Expenditure to Date

Projected Expenditure: \$3,060,000

Actual Expenditure: \$3,060,000