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TITLE: "Dermal Coverage of Traumatic War Wounds"

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14. ABSTRACT The proposed study is a prospective, randomized within-patient controlled feasibility study to evaluate the safety and effectiveness of the ReCell Device for re-epithelialization of full thickness wounds treated with INTEGRA MBWM. The ReCell Device is a stand-alone, battery operated cell separation device that enables preparation of a cell suspension from a small, thin, split-thickness skin biopsy. The autologous epidermal cell suspension is available for immediate delivery onto a prepared skin surface. This process has the potential to enhance skin regeneration while minimizing donor site morbidity ^{2,3} . The performance of ReCell over INTEGRA MBWM in combination with 1:6 meshed split-thickness skin graft (STSG) will be compared to standard practice control (i.e., 1:1.5 meshed STSG over Integra MBWM). We expect all ReCell-treated and control areas of the wounds to heal adequately. However, we predict areas treated with ReCell will re-epithelialize more quickly than control areas, which has the potential to reduce the risk of infection and scarring in ReCell-treated areas compared to control areas.					
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Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	6
Key Research Accomplishments.....	8
Reportable Outcomes.....	9
Conclusion.....	10
References.....	10
Appendices.....	11
Supporting Data.....	11

INTRODUCTION:

Objectives/Specific Aims/Hypotheses:

Our hypothesis is that subject areas that receive ReCell treatment over a widened mesh STSG over Integra will have healing equivalent to areas treated with a lower STSG ratio over Integra.

The goal of the study described herein is to determine the effectiveness of the use of the ReCell device over a widened STSG mesh will improve upon the current standard of care. The potential for ReCell's promotion of healing in the interstices of the STSG mesh may close gaps that are potential points of failure during later physical activity. Within the current study, each patient will serve as his or her own control, allowing for comparison of ReCell-treated (experimental) and non-ReCell-treated (control) regions of the wound. The specific aims of this pilot clinical study are delineated below.

Specific Aim 1: Evaluate safety of ReCell treatment of full-thickness wounds treated with INTEGRA™ MBWM compared to control site. The safety and tolerability of ReCell treatment relative to standard of care (the control site) will be evaluated during the first 12 weeks after treatment, when the wound is most vulnerable. Safety-related issues will continue to be monitored through 24 weeks after treatment. Patients will be assessed for the following safety issues at each visit:

- Delayed healing/non-healing of wound and donor site
- Graft loss
- Heterotrophic ossification
- Infection
- Scar contracture
- Durability (i.e. abrasions/injuries at graft site due to graft fragility)
- Allergic response to trypsin
- Subject Complaint (pain and itching)
- Vital Signs
- Blood chemistries and hematology
- Other Treatment-related adverse events requiring surgical intervention prior to 12 weeks post-treatment and serious adverse event (SAE) occurrences.

We predict no difference in safety measures between ReCell-treated areas and control areas of the wound.

Specific Aim 2: Assess the **preliminary effectiveness** of ReCell treatment of full thickness wounds treated with INTEGRA MBWM compared to a control site. Preliminary effectiveness will be assessed during an acute healing phase (Weeks 1–6) and will focus on healing of both wound and donor sites.

Acute Healing Evaluations:

1. Wound epithelialization
2. Histology
3. Patient pain rating

We predict that, at each point in time, more ReCell-treated areas will be healed as effective as the control areas of the wound.

Specific Aim 3: Assess the long-term effectiveness of ReCell treatment of full thickness wounds treated with INTEGRA MBWM compared to a control site. Long-term effectiveness will be assessed up to 24 weeks post-ReCell treatment and evaluations will focus on the integrity and durability of regenerated tissue as well as physical characteristics such as pliability and cosmesis. Patient satisfaction will also be evaluated.

Evaluations to be performed include:

1. Scar assessment scale using the Patient and Observer Scar Assessment Scale (POSAS 2)
2. Vancouver Scar Scale
2. Functional outcome rating
3. Patient satisfaction
4. Histology

We predict that scar/functional outcomes and patient satisfaction will be superior for ReCell-treated areas.

The proposed study is a prospective, randomized within-patient controlled feasibility study to evaluate the safety and effectiveness of the ReCell Device for re-epithelialization of full-thickness wounds treated with INTEGRA MBWM. The ReCell Device is a standalone, battery operated cell separation device that enables preparation of a cell suspension from a small, thin, split-thickness skin biopsy. The autologous epidermal cell suspension is available for immediate delivery onto a prepared skin surface. This process has the potential to enhance skin regeneration while minimizing donor site morbidity. The performance of ReCell over INTEGRA MBWM in combination with 1:6 meshed split thickness skin graft (STSG) will be compared to standard practice control (i.e., 1:1.5 meshed STSG over Integra MBWM).

We expect all ReCell-treated and control areas of the wounds to heal adequately. However, we predict areas treated with ReCell will re-epithelialize more quickly than control areas, which has the potential to reduce the risk of infection and scarring in ReCell treated areas compared to control areas.

Timeline:

Patients will be studied for 24 weeks after ReCell treatment. The first 6 weeks comprise of an acute phase focusing on healing and safety assessments. Follow-up visits at 12 and 24 weeks post treatment focus on long-term effectiveness in terms of aesthetic and functional

outcomes, as well as patient satisfaction.

BODY:

Task 1: Receive award; Build research team (Q1-Q2, Nov 2012-Apr 2013)

1a. Hire Program Manager

Hired a Program Director, Christian Walker, and entered a service agreement with The Henry Jackson Foundation (HJF) to support his work. This agreement was effective 01DEC2015.

1b. Hire Clinical Research Coordinator

A Program Manager and a Clinical Research Coordinator were previously hired in Year 1, Quarter 2. Both personnel were replaced with a Clinical Program Manager/Nurse Research Coordinator 05FEB2016 and a Clinical Research Coordinator also listed in the service agreement with HJF.

The team identified and received competitive quotes for the following resources originally assigned to Avita in Year 1, Quarter 2. These external resources can support the study for less than \$110,000. This amount is within the awarded budget:

- Regulatory consulting – Kim Strohkirch, Memphis Regulatory Consultants
- Monitoring – IMARC Research Inc.
- Biostatistics – Dale Glaser, Consultant

Dale Glaser of Glaser Consulting was identified to perform bio statistical analysis for the study in Year 1, Quarter 4. Biostatistics consultant, Dale Glaser, performed additional tasks in Year 2, Quarter 2, including discussing the power and design for the ReCell device study, conducting power analysis, summarizing results, writing up proposed analysis, and also adding comments to the revised protocol.

Task 2: IDE preparation and submission (Q1-Q5, Nov 2012-Jan 2014)

2a. Identify IDE sponsor

J. Peter Rubin MD at the University of Pittsburgh was previously identified as the IDE Sponsor in Year 1, Quarter 3. A robust clinical monitoring plan has been completed that will ensure real time oversight by Dr. Rubin.

2b. Preparation of IDE

The IDE was previously drafted by the regulatory consultant Kim Strohkirch of Memphis Regulatory Consultants in Year 1, Quarter 2. The IDE was drafted based on cross-referencing of the Avita Medical IDE for the multicenter partial thickness burn pivotal IDE study (<http://clinicaltrials.gov/ct2/show/NCT01138917>). WRNMMC and UPitt had a conference call with Kim Strohkirch of Memphis Regulatory Consultants on 29MAY2014 to address outstanding questions and finalize aspects of the IDE. The investigators at WRNMMC and UPitt had a subsequent

conference call on 24JUN2014 to review IDE text. The IDE was finalized and submitted to the University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee and the FDA for approval on 31JUL2014.

2c. Request for 12 month no-cost extension (NCE)

The request for a 12 month no-cost extension with a revised Statement of Work (SOW) was submitted to the Sponsoring agency in Year 1, Quarter 4 and received approval on 27MAR2014.

2d. Contracting and approval by UPMC

A subaward agreement with the University of Pittsburgh was executed 1FEB2014.

2e. IDE review and approval by University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee

The revised Statement of Work was approved by the sponsor. The IDE was finalized and submitted to University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee and the FDA for approval on 31JUL2014.

2f. Submission of IDE

- FDA will respond in 30 days
- Response to FDA questions within 2 weeks
- FDA will have another 30 days to respond.

Kim Strohkirch of Memphis Regulatory Consultants assisted in finalizing the IDE application. The IDE was finalized and submitted to University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) IND/IDE Committee and the FDA for approval on 31JUL2014. Conditional IDE approval from FDA received 29AUG2014. IDE approval received from FDA on 13NOV2014.

2g. IDE received for feasibility study

Final FDA approval of the IDE received 21JAN2015

Task 3: IRB, CRADA and facility approvals (Q3-Q7, May 2013-July 2014)

3a. CRADA

The CRADA between Geneva and Walter Reed National Military Medical Center was fully executed on 23FEB2015.

3b. WRNMMC IRB Coordinating and Site Protocols Preparation & Submission following FDA IDE Approval

Protocol submitted to Kim Strohkirch of Memphis Regulatory Consultants for development of IDE application and the University of Pittsburgh for their development of a site-specific protocol on 17APR2014. Scientific review was successfully completed at WRNMMC on 08MAY2014 with minimal concerns or revisions. Administrative review was completed in 22OCT2014. Protocol was submitted to the WRNMMC IRB 28OCT2014 and reviewed by the IRB on 20NOV2014. Protocol received WRNMMC IRB approval on 09DEC2014.

3c. WRNMMC IRB Coordinating and Site Protocols Approval

IRB approved 09DEC14

IRB approval of Amendment #1 28JAN2015

IRB approval of Amendment #2 07OCT2015

- Including change of PI from Dr. Fleming to Dr. Nesti

3d. HRPO WRNMMC Coordinating and Site Approval

HRPO approved 4FEB2015

HRPO approval of Amendment with change of PI 16OCT2015.

3e. UPITT IRB External Site Protocol Submission

UPITT IRB external site protocol submitted as of 31OCT2015.

3f. UPITT IRB External Site Approval

UPITT IRB external site approval received as of 30NOV2015.

3g. HRPO External Site Approval

HRPO external site approval received FEB2016.

Task 4: Patient Enrollment (Q8-Q18, Aug 2014-Apr 2017)

#Clinical Patients: 20

Patient Enrollment has started with 1st patient enrolled on 20OCT2015 and receiving treatment on 21OCT2015.

Task 5: Patient Follow-up (Q9-Q20, Nov 2014-Oct 2017)

#Clinical Patients: 20

Patient Follow-up of first subject conducted on week 1, 2, 3, 4, and 6 as outlined in the protocol. The week 12 follow-up was not completed as per protocol due to sponsor clinical hold status placed on protocol Jan 2016. After receiving IRB approval, only the scheduled biopsy sample was collected at this visit. Patient Follow-up has started subsequent to the 1st enrolled patient who received treatment on 21OCT2015.

Task 6: Histology/Pathology (Q8-Q20, Aug 2014-Oct 2017)

#Tissue Samples: Up to 110

Histology/Pathology of tissue samples has started as of 21OCT2015 for 1st enrolled patient. Biopsy collected in the OR. Follow-up biopsies collected on week 2, 4, and 12 as outlined in the protocol.

Task 7: Final Report (Q20, Nov 2017-Jan 2018)

7a. Review of data and generation of final report

Data reviewed by UPITT Research Monitor 20-23 APR16.

KEY RESEARCH ACCOMPLISHMENTS:

- Staff Recruitment:
 - Hired a Program Director/Manager and a Clinical Research Coordinator.
- Executed a consulting agreement with James Holmes II, MD of Wake Forest University

who provided feedback on protocol.

- Executed a vendor agreement with Annapath who performed histology services for the study.
- The master CRADA between WRNMMC and Geneva was in effect. A subaward agreement with the University of Pittsburgh was executed.
- IDE preparation and submission:
 - Conditional IDE approval from FDA received 29AUG2014. Final IDE approval received from FDA after report date on 13NOV2014. Final FDA approval of the IDE received 21JAN2015
- IRB package preparation and finalization:
 - Administrative review was completed in 22OCT2014
 - Protocol was submitted to the WRNMMC IRB 28OCT2014 and reviewed by the IRB on 20NOV2014
 - IRB approved 09DEC14
 - IRB approval of Amendment #1 28JAN2015
 - IRB approval of Amendment #2 07OCT2015 including change of PI from Dr. Fleming to Dr. Nesti
- HRPO WRNMMC Coordinating and Site Approval:
 - HRPO approved 4FEB2015
 - HRPO approval of Amendment with change of PI 16OCT2015.
- UPITT IRB external site protocol submitted as of 31JUL2015.
- Investigators, Drs. Nesti and Martin, received training on the use of the ReCell spray-on skin device prior to its use for 1st enrolled patient on 20OCT2015. Andrew Quick, the Vice President of Research and Technology at Avita Medical, the manufacturer of the ReCell device, provided the investigators' training in person.
- Patient Enrollment has started with 1st patient enrolled on 20OCT2015 and receiving treatment on 21OCT2015.
- Patient Follow-up has started subsequent to the 1st enrolled patient who received treatment on 21OCT2015.
- Histology/Pathology of tissue samples started as of 21OCT2015 for 1st enrolled patient.

REPORTABLE OUTCOMES:

There are no reportable outcomes to report.

CONCLUSION:

The GOR (Dr. Mary Alice Woody) recommended termination of this project on 8JUN2016. The Geneva Foundation concurred with termination or transfer of the project on 29JUL2016. The GOR/USAMMDA and USAMRAA concurred with Geneva's recommendation on 10AUG2016. A termination modification was provided with an effective date of 15OCT2016 on 29SEPT2016.

REFERENCES:

PubMed ReCell search performed Nov 26, 2013 yielded the following reports that have been published since the submission of the proposal

Lim J, Liew S, Chan H, Jackson T, Burrows S, Edgar D, Wood F. "Is the length of time in acute burn surgery associated with poorer outcomes?" *Burns* (2013), <http://dx.doi.org/10.1016/j.burns.2013.06.005>

Park J, Heggie K, Edgar D, Bulsara M, Wood F. "Does the type of skin replacement surgery influence the rate of infection in acute burn injured patients?" *Burns* (2013) 39(7):1386-1390, <http://dx.doi.org/10.1016/j.burns.2013.03.015>

O'Neill T, Rawlins J, Rea S, Wood F. (2012) "Complex chemical burns following a mass casualty plant incident: How optimal planning and organisation can make a difference." *Burns* 38: 713-718.

Wood FM, Giles N, Stevenson A, Rea S, Fear M. "Characterisation of the cell suspension harvested from the dermal epidermal junction using a ReCell® kit." *Burns* (2012), 38(1):44-51.

Campanella SD, Rapley P, Ramelet AS. "A randomised controlled pilot study comparing Mepitel® and SurfaSoft® on paediatric donor sites treated with Recell®." *Burns* (2011) Dec;37(8):1334-42.

Anderson JR, Fear MW, Phillips JK, Dawson LF, Wallace H, Wood FM, Rea SM. "A preliminary investigation of the reinnervation and return of sensory function in burn patients treated with INTEGRA®." *Burns* (2011) Nov;37(7):1101-8.

Gravante G, Di Fede MC, Araco A, Grimaldi M, De Angelis B, Arpino A, Cervelli V, Montone A. "A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns." *Burns* (2007) Dec;33(8):966-72.

APPENDICES:

Attach all appendices that contain information that supplements, clarifies, or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, surveys, etc.

SUPPORTING DATA:

All figures and/or tables shall include legends and be clearly marked with figure/table numbers.