

AWARD NUMBER: W81XWH-13-2-0031

TITLE: Autologous Skin Cell Spray for Massive Soft Tissue War Injuries: A Prospective, Case-Control, Multicenter Trial

PRINCIPAL INVESTIGATOR: CDR Mark Fleming

CONTRACTING ORGANIZATION: The Geneva Foundation  
Tacoma, WA 98402

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Command Fort Detrick, Maryland 21702-5012

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| <b>14. ABSTRACT</b><br>The goal of this research is to assess the success of skin cell spray combined with a biocomposite subcutaneous (INTEGRA) layer for repair of large open wounds. The objective is the treatment of extremity skin and soft tissue defects with an autologous skin cell spray transplantation in combination with dermal regenerative matrices (Integra). In this <u>case control randomization design</u> , after all patients are treated with dermal matrix, patients will be <b>randomized</b> to Arm 1 (control group; standard skin grafting with 1:1.5 meshing); Arm 2 (experimental group 1; wide 1:6 mesh graft with sprayed cells), and Arm 3 (experimental group 2; sprayed cells only, no graft). To measure the outcome of specific aim 1, all patients will be assessed with serial photography, range of motion testing, functional limb use, and objective measures of gross wound healing (wound size measurements and Image J analysis), as will healing on the cellular level (serial post-graft biopsies). Patients will be followed for 6 months after treatment to define long-term outcomes. |
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| <b>15. SUBJECT TERMS</b><br>Spray skin, Bioartificial dermis, Soft tissue coverage, Traumatic wounds, Regenerative medicine |
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## 1. INTRODUCTION:

Massive skin and soft tissue injuries of the extremities are common among battle-injured soldiers, often resulting in significant skin deficits. These wounds are routinely treated with a layer of skin taken from an intact donor area of the injured patient's body and grafted over the wounded area to obtain a healed wound. These skin grafts are often "meshed" or flattened and spread out to increase the size of the skin graft to better cover a large wound. Standard "meshing" increases the size of the donor graft by 1.5 times (1:1.5). Problems with healing and skin irritation remain with such skin grafts when the injured areas are large or deep. Additionally, large graft donor sites may be required to cover the injury. New ways to deal with skin and soft tissue injuries in the war wounded are needed.

We are conducting a three-arm clinical trial. Patients will be randomized to one of three ARMS: ARM 1 will receive standard meshed skin graft, 1:1.5; ARM 2 will receive a wide meshed skin graft, 1:6 with sprayed cells; and ARM 3 will receive sprayed cells alone without meshed skin graft.

The goal of this research is to assess the success of skin cell spray combined with a biocomposite subcutaneous (INTEGRA) layer for repair of large open wounds.

Walter Reed National Military Medical Center (WRNMMC) and the University of Pittsburgh (UPITT) will collaborate to conduct this study. A total of 66 adult participants from both WRNMMC (45) and UPITT (21), male or female, ages 18 years of age and older with wounds requiring skin grafts will be asked to participate. While the study is open to civilians, patient recruitment will be highly focused on wounded warriors.

While there are no guarantees in medicine or in research, it is possible that the participant may directly benefit from this study. There is a possibility that graft donor sites may be lessened for some patients and skin grafts over wounds may have an improved appearance. These potential results may increase the participant's ability to comfortably use the extremity thus resulting in an increase in the participant's activities of daily function.

## 2. KEYWORDS:

Spray skin, Bioartificial dermis, Soft tissue coverage, Traumatic wounds, Regenerative medicine, Combat wounds, Full-thickness skin loss

## 3. OVERALL PROJECT SUMMARY:

### Statement of Work

#### Objectives:

- 1) The treatment of extremity skin and soft tissue defects with an autologous skin cell spray transplantation in combination with dermal regenerative matrices (Integra). In this case control randomization design, after all patients are treated with dermal matrix, patients will be **randomized** to Arm 1 (control group; standard skin grafting with 1:1.5 meshing); Arm 2 (experimental group 1; wide 1:6 mesh graft with sprayed cells), and Arm 3

(experimental group 2; sprayed cells only, no graft). To measure the outcome of specific aim 1, all patients will be assessed with serial photography, range of motion testing, functional limb use, and objective measures of gross wound healing (wound size measurements and Image J analysis), as well as healing on the cellular level (serial post-graft biopsies). Patients will be followed for 6 months after treatment to define long-term outcomes.

- 2) The assessment of biologic properties of the cells processed for spraying and correlate with clinical outcomes. This will include epidermal progenitor cell and dermal stromal cell yield, cell proliferation, capacity for differentiation, and cell sub-population analysis by multiparameter flow cytometry. Results of these assays will be correlated with speed and quality of wound healing to search for predictors of good clinical outcome.

In the original proposal, the University of Pittsburgh committed to providing cell isolation services associated with the use of a purchased skin gun from Stem Cell Systems Inc. under the direction of Dr. Jorg Gerlach. This scenario has served as the foundation for achieving our deliverables up until the past performance period when Dr. Gerlach announced that SCS sold the IP rights to the skin gun technology to a US based company, Renovacare, and that Renovacare would now be the preferred vendor for obtaining the skin gun device and the necessary documentation to support the IDE application. With this in mind, the University proceeded and shifted its contract negotiations from SCS to Renovacare. During this process, the University conducted its due diligence on Renovacare and discovered (without disclosure from Dr. Gerlach) that Dr. Gerlach had sold his IP rights for the cell isolation process to Renovacare in July 2013 in exchange for a substantial cash payout tied to the deliverables of the skin gun award. The University immediately presented Dr. Gerlach with their findings and stopped all negotiations with Renovacare and ceased Dr. Gerlach's contributions to the grant until a conflict management plan could be developed and executed that would comply with both the University and federal guidelines. In early March the University determined that a resolution to the conflict could not be achieved and removed Dr. Gerlach from the grant thus leaving a void in technical expertise related to the University's obligations with the project. The University made Geneva Foundation personnel and Walter Reed PIs aware of the conflict and its inability to execute a conflict management plan and thus had Dr. Gerlach removed from the project. Furthermore, the University informed them that there was now no direct legal connection for the use of the cell isolation process and that IP rested with Renovacare who is not a third party to the current contract.

Upon stopping the negotiations with Renovacare, Renovacare approached the Geneva Foundation to determine if an agreement could be established with them as opposed to the University of Pittsburgh. In doing so, the CEO of Renovacare presented the Geneva Foundation with three specific terms that they wished to be included in an agreement for the use of the cell isolation process and for the purchase of the skin gun device. They included:

1. Renovacare would own all IP that resulted from the study
2. Renovacare would have exclusive rights the data generated from the study for their use in future work
3. Renovacare would have the right to appoint "Renovacare Approved" personnel for the study.

These terms were then reviewed by Geneva and presented to the sponsor for comment. In mid-March the sponsor shared its position on each of the above terms with Geneva and the PIs, Geneva then shared those positions with Renovacare. In response to those positions, Renovacare has since requested a copy of the contract so it can review the terms for participating as a vendor for the required services.

At the same time that Geneva and Pitt were working through the issues with Renovacare and continuing to try and find solutions to the obstacles presented, the Walter Reed PIs determined that they needed to identify an alternative approach to fulfilling the objectives of the award and do so in a very timely manner. Therefore the PIs identified another skin device and cell isolation/expansion process that may fit with the study plan and approached the company and scientists associated with the alternative technology. It was determined that the alternative approach could work and that the company was somewhat interested in pursuing the possibility of participating. The PIs briefed the sponsor of these discussions and the sponsor endorsed the PI's pursuit of an alternative technology.

No activity in regards to the scientific aims has occurred during this reporting period due to the challenges and subsequent "Stop" work order placed on the University of Pittsburgh as of March 15, 2014 while Geneva, WRNMMC and Sponsor worked to find a solution.

During this time, the status of the project was:

- The University of Pittsburgh has informed the Geneva Foundation of its conflicts and was in process of making financial restitution for all expenses incurred by Dr. Gerlach during the period that the conflict was not disclosed.
- The University of Pittsburgh had received a revised Statement of Work from the Principal Investigator, Dr. Fleming, and Dr. Rubin and Avita who have each provided their collaborative scientific input.
- A meeting via conference call was conducted between the investigators at Walter Reed, the University of Pittsburgh and Avita to discuss the revised SOW with all partners on the project.
- An alternative technology was identified as Avita's ReCell spray skin device while we awaited Sponsor approval.
- The revised SOW and a table outlining the differences between the two spray skin studies were sent to the sponsor on 15 Sept 2014.

#### **4. KEY RESEARCH ACCOMPLISHMENTS:**

Task #1A – External Site Clinical Investigation & Cell Expansion (University of Pittsburgh) – pending approval of the revised Statement of Work will be modified

##### **A. Develop Final Study Protocol (months 0-5)**

The IDE must be approved by the FDA before any and all protocols can be reviewed and approved either at WRNMMC or at Pitt. The overall study protocol will be developed and written by WRNMMC as the coordinating center and then sent to the University of Pittsburgh for inclusion into their site specific protocol. The University of Pittsburgh cannot submit the protocol to the IRB, until the WRNMMC master protocol has been approved by WRNMMC's IRB Oversight Committee and DoD HRPO. The protocols have been initially drafted but are not yet finalized for submission.

B. Detailed Budget Review and Implementation (months 0-5)

The University of Pittsburgh has completed a detailed budget review with each investigator. Originally, budgetary gaps for financing Post-doc, technicians, and travel of the Gerlach Group were identified and resources were being investigated to fill those gaps. However, due to the conflict that has arisen, the work at the University will not be proceeding under the direction of Dr. Gerlach and the University is waiting for a decisions from the PIs as to the pathway they wish to use to fulfill the scientific obligations associated with the skin gun and cell isolation process.

C. Organize Team and Facilities (months 0-6)

The University of Pittsburgh has organized its clinical and investigative teams and is presently on hold with all tasks secondary to above mentioned technology issue within section one. Bi-weekly conference calls between WRNMMC, UPITT, Geneva and IMARC are on hold. The PI has allocated the appropriate resources including clinical operations and application, scientific oversight, and project and administrative management to execute the task once the hold released.

D. IDE Submission and Approval (months 0-6)

Pending approval of the revised Statement of Work, Avita will now sponsor the IDE and cross-reference their existing IDE, which should expedite the approval process.

Dr. Rubin will no longer be the holder of the IDE, and Dr. Gerlach has been removed from the study as a sub-investigator as a result of his conflict.

E. Regulatory Approval (months 6-12)

Regulatory approval has not yet been achieved. FDA and IRB approvals are not expected to be obtained until the new SOW is implemented and the team is reinstating its activities.

F. Subject Recruitment (months 12-35)

Subject recruitment has not yet begun. A complete recruitment plan will be provided prior to the start of this process.

G. Initiate Clinical Study Including Cell Isolation (21 subjects) (months 12-36)

The clinical study will begin after all regulatory approvals have been granted. There is now a change in the expected delivery date for activities related to this task and a new procedure will be identified in the revised Statement of Work.

Task #2 – Data Management (University of Pittsburgh)

A. Source and CRF Development (months 9-12)

Source and CRF forms will be developed simultaneously with the clinical protocol by WRNMMC team. All procedures for complying with regulatory policies in regards to data management have been reviewed and will support Pitt as the holder of the IDE for this study.

B. Database Design and Development (months 9-12)

The University of Pittsburgh has an existing clinical database and process for capturing clinically relevant data. This database would be used and the processes for capturing information will be shared with all appropriate parties.

C. Transcription, Data Entry and Verification (months 15-36)

Not implemented as of 30 December 2014.

D. Data Monitoring and Cleaning (months 15-36)

Not implemented as of 30 December 2014.

E. Analysis/Data Preparation (months 25-36)

Not implemented as of 30 December 2014.

All work suspended as of March 15, 2014.

## 5. CONCLUSION:

### **Military Benefit**

Massive skin and soft tissue injuries are common challenges within the battle injured multiple extremity amputees. Studies suggest that significant soft tissue loss is one of the most frequently encountered associated injuries. Furthermore, these soft tissue losses can directly lead to a compromise in the maintenance of a functional limb length. Currently, the standard treatments for segmental tissue loss in amputations include a combination of the following procedures: limb shortening to assist in stump closure, free tissue transfers, pedicle flaps, local tissue rearrangements, and/or autograft split thickness skin grafting typically in conjunction with dermal substitutes. However, these procedures may result in decreased functional limb lengths, significant donor site morbidities, and non-durable surface areas prone to erosive wear with prosthetic use. Moreover, as a number of our wounded warriors have multiple limb injuries and amputations, the common accepted donor sites for autologous tissues, specifically skin, are becoming increasingly limited.

The Walter Reed National Medical Center serves a population that includes a high volume of our wounded warriors from all branches of the Armed Forces. The treatment options rendered as a part of this study will replicate the level of care these patients would otherwise receive, while also allowing us to study each different alternative under controlled guidelines in an effort to advance treatment for our wounded. The proposed study can result in an immediate impact on the standard of care for full thickness soft tissue loss by helping to establish best practices and thereby maximizing the patients recovery while minimizing possible complications and costs (monetary and physical), while also providing a valuable and durable soft tissue coverage for those wounded warriors that may have very limited available soft tissue donor sites.

Our proposed technique for skin-cell spray transplantation has been employed in both Berlin, Germany and in Pittsburgh, PA for successful treatment of burn related injuries within feasibility studies. Based on preclinical and early clinical results, the short-term benefits of this study will include potential viable and readily available regeneration of necessary autologous skin to place on a dermal regenerate in massive soft tissue injuries seen in our war wounded. This clinical model would be the first to potentially show the benefit of the skin cell spray gun treatments in traumatic wounds, outside of burn

patients. The benefits can also be extrapolated to complex traumatic civilian injuries that likewise pose significant issues with available autologous skin coverage (e.g. necrotizing fasciitis, motor vehicle accidents or other trauma with associated soft tissue avulsion injuries, etc.). Important data on the mechanism of action, refinements of technique, expansion of the device and technique to future applications, and most importantly, technology transfer throughout WRNMMC, associated Military Treatment Facilities (MTFs), and civilian or academic centers is of great interest.

**6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:**

Nothing to report.

**7. INVENTIONS, PATENTS AND LICENSES:**

Nothing to report.

**8. REPORTABLE OUTCOMES:**

Nothing to Report.

**9. OTHER ACHIEVEMENTS:**

Nothing to report.

**10. REFERENCES:**

Nothing to report.

**11. APPENDICES:**

Termination Memo

## Linzie Wagner

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**Subject:** Cooperative Agreement No. W81XWH-13-2-0031, CDMRP Log# OR110216  
(UNCLASSIFIED)  
  
**Importance:** High

Classification: UNCLASSIFIED  
Caveats: NONE

Good afternoon, Ms. Wagner.

Reference:

Title: "Autologous Skin Cell Spray for Massive Soft Tissue War Injuries: A  
Prospective, Case-Control, Multicenter Trial"  
Principal Investigator: Dr. Mark Fleming at Walter Reed National  
Military Medical Center  
Contracting Organization: Geneva Foundation

The Grants Officer's Representative and Science Officer have reviewed the revised statement of work submitted on 15 September 2014 for the subject proposal. Based on their review, it has been determined to be in the best interest of the Government to terminate this study based on the following:

1. The originally proposed study is no longer feasible as the electronically controlled skin cell spray device with unique cell isolation technique to prepare the skin spray is not available.
2. The alternate proposed study utilizing the ReCell device is already being conducted by the same PI under the management of personnel at USAMMDA with DoD funds.
3. While there is a minor difference between the USAMMDA clinical trial (W81XWH-13-2-0004) and the alternate clinical trial design the PI is proposing, it is not significant to warrant a separate clinical trial in parallel. A significant portion of the two studies will be in duplication.
4. Finding the military subjects could be another obstacle as the war is closing down.
5. The USAMMDA ReCell study is significantly behind schedule and, in over a year and half, the PI has not been able to secure HRPO approval.

Based on the information above, please provide your agreement to terminate this grant. Your response is required by COB on Wednesday, November 5th. We will then proceed with a modification to terminate the award and de-obligate the funding.

Regards,

Dana L. Herndon

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Caveats: NONE