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AWARD NUMBER: W81XWH-13-2-0031

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

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14. ABSTRACT 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 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 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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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.

KEYWORDS:

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

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 will 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.

Progress and Results

Tasks and Subtasks:

Task #1 – Clinical Investigation & Cell Expansion (WRNMMC) (Q1/2013 – Q1/2016)

- a) Develop Final Study Protocol (Q1/2013 – Q2/2013)
 - The IDE must be approved before any and all protocols can be reviewed and approved either at WRNMMC or at UPitt. The protocol is being developed in collaboration with UPitt and will be finalized for submission at WRNMMC's IRB Oversight Committee and HRPO.
- b) Detailed Budget Review and Implementation (Q1/2013 – Q3/2013)
 - The Geneva Foundation has completed a detailed budget review. MIPR POC at WRNMMC has been identified.
- c) Organize Team and Facilities (Q1/2013 – Q3/2013)
 - The PI and team have organized its clinical and investigative teams and are moving forward with all tasks. The PI has allocated the appropriate resources including clinical operations and application, scientific oversight, and project and administrative management to execute the task.

- d) Regulatory Approval (Q1/2013 – Q3/2013)
 - WRNMMC team is communicating with UPitt on the preparation of the IDE. The IDE application is being populated with information in support of an FDA approval.
- e) Subject Recruitment (Q3/2014 – Q1/2015)
 - To date subject recruitment has not begun. A complete recruitment plan will be provided prior to the start of this process.
- f) Initiate Clinical Study including Cell Isolation and Expansion (45 subjects) (Q4/2013 – Q1/2015)
 - The clinical study will begin after all regulatory approvals have been granted.

Task #1A – External Site Clinical Investigation & Cell Expansion (University of Pittsburgh) (Q1/2013 – Q1/2016)

- a) Develop Final Study Protocol (Q3/2013 – Q4/2013)
 - 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 complete and submit the IRB protocol until it 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 (Q3/2013 – Q4/2013)
 - The University of Pittsburgh has completed a detailed budget review with each investigator. Budgetary gaps for financing Post-doc, technicians, and travel of the Gerlach Group, will now be addressed by Pitt resources and potentially met by the co-sponsorship of an SCS partner, Vector Asset Management, Vancouver (VAM) / RenovaCare (RC). However, this will need to be reviewed once more after an alternative pathway has been established.
- c) Organize Team and Facilities (Q4/2013 – Q1/2014)
 - The University of Pittsburgh has organized its clinical and investigative teams and is moving forward with all tasks. Weekly conference calls between WRNMMC, UPITT, Geneva and IMARC have been implemented to monitor project progression. The PI has allocated the appropriate resources including clinical operations and application, scientific oversight, and project and administrative management to execute the task.
- d) IDE Submission and Approval (Q1/2013 – Q1/2014)

- The IDE application is being populated with information in support of an FDA approval. Patsy Simon has developed and circulated the second draft of the application and is awaiting input from Walter Reed, IMARC and from internal members of the University of Pittsburgh team. Weekly conference calls between WRNMMC, UPITT, Geneva and IMARC have been implemented to monitor project progression. These meetings are productive for team review and provide input as to the status of assigned components. The Coordinating Center (WRNMMC) and the regulatory consultant have provided guidance on the required components for the submission of the IDE application. Requests have been made for the device manufacturer to provide information needed to complete the required manufacturing section of the IDE (i.e. cell isolation SOP). She is guiding them on what is needed to support the manufacturing components and the cell isolation kit of the IDE. In addition the IDE application will contain the device design history file which will be provided by the device manufacturer.
 - Dr. Rubin will be the principal sponsor of the IDE (with primary responsibility).
- e) Regulatory Approval (Q4/2013 – Q1/2014)
- Regulatory approval has not yet been achieved. FDA and IRB approvals are not expected to be obtained until the first quarter of year two of the project. This is projected to be a three month delay from the original project plan. Steps are being taken to minimize the delay and anticipate any future challenges that may arise.
- f) Subject Recruitment (Q1/2014 – Q2/2015)
- 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 and Expansion (21 subjects) (Q1/2014 – Q2/2015)
- The clinical study will begin after all regulatory approvals have been granted.

Task #2 – Data Management (University of Pittsburgh) (Q1/2013 – Q1/2016)

- a) Source and CRF Development (Q1/2013 – Q2/2013)
- Source and CRF forms will be developed simultaneously with the clinical protocol. 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 (Q2/2013 – Q3/2013)

- 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 (Q3/2013 – Q1/2016)
 - Not yet implemented.
- d) Data Monitoring and Cleaning (Q3/2013 – Q1/2016)
 - Not yet implemented.
- e) Analysis/Data Preparation (Q3/2014 – Q4/2014, Q3/2015 – Q4/2015)
 - Not yet implemented.
- f) Analysis/Data (Q1/2015 – Q2/2015, Q4/2015 – Q1/2016)
 - Not yet captured.

Task #3 – Education and Training (WRNMMC/University of Pittsburgh) (Q1/2013 – Q1/2016)

- a) Create a teaching compendium (Q1/2013 – Q2/2013)
 - Not yet implemented.
- b) Training and Knowledge Transfer (Q1/2013 – Q2/2013)
 - Not yet implemented.
- c) Manuscript Development and Publish (Q1/2015 – Q2/2015, Q4/2015 – Q1/2016)
 - Not yet implemented.
- d) Industry Presentations (Q3/2014 – Q4/2015)
 - Not yet implemented.

Discussion

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 Renovcare 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. Geneva takes delivery of all materials (hardware and documentation) by way of a Purchase Order.
2. Renovacare would own all IP that resulted from the study
3. Renovacare would have exclusive rights the data generated from the study for their use in future work
4. 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 fulfill 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 interested in pursuing the possibility of participating. The Walter Reed PIs and Geneva had a conference call with the sponsor on 6March2014 to discuss these discussions. The PIs briefed the sponsor of these complications and the sponsor endorsed the PI's pursuit of an alternative technology.

The current status of the project is as follows:

- The project at the University of Pittsburgh is under a cease work order until further notice.
- The University of Pittsburgh has informed the Geneva Foundation of its conflicts and is waiting for a response and direction as to what action needs to be taken.
- The PIs will continue to perform due diligence on identifying an alternative technology will satisfy the original intent of the proposal and will develop a new statement of work by 30April2014.

The IDE application drafting presently is on hold until an alternative technology determination is decided upon by the PIs.

Current Problems/Issues:

- The University of Pittsburgh discovered a conflict between Dr. Gerlach and Renovacare which cannot be resolved so the University has removed Dr. Gerlach from the project thus leaving a gap in scientific aspects of the project.
- The University has temporarily stopped discussions with Renovacare until Geneva can determine if they will contract directly with Renovacare or if an alternative technology will be used.

Anticipated Problems/Issues:

- Regardless of the manufacturer selected, there will be a delay in obtaining information for the IDE until contracts get executed between the new manufacturer and the appropriate team members.

Resolution Actions/Plans:

- Identification of alternative technology and new pathway forward that will meet the scientific requirements of this project and satisfy the original intent of the proposal.
- Submission of plan to the sponsor outlining the new pathway forward by 30April2014.
- Execution of contracts between the new manufacturer and the appropriate team members and obtain information for the IDE.

KEY RESEARCH ACCOMPLISHMENTS:

WRNMMC

- Staff Recruitment:
 - Hired a Program Director/Manager, a Clinical Research Coordinator and a Research Assistant.
- Clinical Safety Monitor identified as Carlton Brown, MD.
- Identification of IMARC Research as the regulatory monitor for this study, contracted by Geneva Foundation in coordination with the University of Pittsburgh and WRNMMC.
- Weekly conference calls with Pittsburgh team have been held throughout the year.
- Clinical protocol has been drafted and is in revision prior to submission to University of Pittsburgh O3IS office, incorporation into the IDE for submission to FDA, and IRB submission at University of Pittsburgh and WRNMMC.
- IRB package preparation:
 - Draft protocol, informed consent and CRFs are being finalized.
 - Finalization will be performed upon approval of the clinical trial plan by the sponsor.
 - IRB package will be submitted following submission of the IDE and receipt of the IDE login number.
- Identification of alternative technologies that will meet the scientific requirements of this project.

Pittsburgh

- The Pitt team developed project task list and timeline for completion of objectives.
- Met with co-investigators device manufacturer and discussed the components of IDE application and have assigned responsibility for the completion of each section by the appropriate group and/or person.
- Dr. Rubin made a site visit to Stem Cell Systems (SCS) GmbH in Berlin Germany.
- Dr. Gerlach built a spray gun prototype with Stem Cell Systems.
- Dr. Gerlach obtained a free spray gun prototype for testing and verification of cell spray patterns on skin from SCS. Dr. Gerlach conducted due diligence with spray

gun design and tested spray gun device from SCS to ensure applicability and verification of cell spray patterns.

- Manual spray gun device performed in a similar manner to the electronic version. Cell spray patterns are consistent with the electronic spray patterns.
 - The spray gun device is compatible with standard operating room connections and proper airflow can be generated to support the device.
 - Regulatory documentation in support of the manual spray device was to be completed by Stem Cell Systems upon execution of a purchase order from the University of Pittsburgh and WRNMMC.
 - Dr. Gerlach and his investigative team were to conduct the cell isolation process as a service for the study. SCS was to prepare materials and documentation for the administration process to support the FDA submission.
- Finalized investigation of the air handling systems by Dr. Gerlach's team.
- Finalized investigation of wound covering components for the surgical dressings post spray gun applications.
- Investigated the ETO sterilization process for each subject use of the spray gun for standardized cleaning and assembly.
- Patrick Cantini requested revised pricing quotes from spray gun manufacturer SCS to ensure compliance with University of Pittsburgh purchasing policies and to separate all Pitt purchases from WRNMMC.
- Pasty Simon, RN, BS, CCRC investigated (under Dr. Rubin's guidance) the option of Pitt holding the IDE on behalf of WRNMMC for this project. The University of Pittsburgh O3IS office found this to be appropriate with Dr. Rubin as an acceptable holder of the IDE at Pitt. O3IS will submit IDE version draft with attention to Project monitoring and real time safety reporting to committee for review and approval prior to initiating project at the University of Pittsburgh.
- Marla Harris worked with the Geneva Foundation to finalize the sub-contract between Geneva and the University of Pittsburgh.
- Patrick Cantini communicated with Stem Cell Systems (device manufacturer) and discussed the language used in the two agreements (Sub-Agreements w/an SOW and an MTA). Patrick requested SCS to comment on a Statement of Work which was provided to them on November 20, 2013. The SOW was the main component to define the Sub-Agreement, which Pitt was drafting to forward to SCS for execution. SCS replied that they would prefer to oversee the entire package of legal documents prior to working on individual components such as the SOW. A MTA was being drafted by Pitt to send to SCS for execution but was not delivered to/executed by SCS.

- Patrick Cantini was incorporating the newly announced partnership of Vector Asset Management, Vancouver (VAM) to Stem Cell Systems into the contract negotiations. By January 2014, VAM established a US company based in New York, NY. The name of the US subsidiary is RenovaCare Inc. (RC) and RC overtook the entire skin activities from VAM. While SCS will continue to develop SOPs, prototypes and producing the devices for RenovaCare, the IP on the skin gun device and the skin cell isolation SOP's was transferred to RC. VAM has previously suggested to sponsor the study for \$120,000 and the Geneva Foundation was overseeing discussions between Pitt and VAM on a sponsoring agreement to accept that financial input. This support of \$120,000 was to include \$60,000 overhead of Pitt and the remaining \$60,000 was to fill the project financing gap of Dr. Gerlach's lab. VAM meanwhile suggested to also contribute to the study by delivering the skin gun devices produced by SCS to the project at no cost to avoid the waiting time for the legal interactions with Pitt on the any purchase agreement and a MTA. VAM, Geneva Foundation and Pitt were discussing a sponsoring agreement for obtaining the \$120,000 and VAM suggested to include the devices into this agreement, rendering all other agreements not necessary anymore. The receipt of the devices at no cost would have also increased the available budget for Walter Reed and Pitt during the course of the study.

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.

Transition Plan

A major goal of this study will be to generate a validated treatment protocol that can be applied/shared at hospital sites throughout the Department of Defense system as well as civilian institutions. As such, a teaching compendium of case reports, video clips, and technical instructions will be produced. Once the study is complete, the investigators and collaborating military physicians will meet to review the data and generate a standardized treatment protocol that can be broadly applied.

This technology will be quite easy to transfer, once validated. The equipment is commercially available, the surgical skills needed fall within the scope of practice for most surgeons who treat soft tissue trauma, and the technology can be used in almost any surgical facility. The learning curve for the instrumentation and technique will not be a barrier to use for most surgeons. The development of dedicated teaching tools and a preceptor system to be made freely available to any surgeon will be undertaken. The funding strategy that will be used to bring the outcomes to the next level of delivery to the military or civilian market includes further development of our industry collaboration. Once we have identified a significant improvement with spray skin grafts, we will disseminate our results and apply the technique throughout all hospitals in the DoD system.

Plan for Technology Transfer for Broad Use among Physicians who Treat Full Thickness Soft Tissue Wounds:

1. **Direct interaction with surgical collaborators at major military hospitals that treat extremity trauma.** Drs. Fleming and Valerio will work with Dr. Rubin during the course of the study to transfer the technology for broad use within the military medical community.
2. **Assistance from military surgical collaborators in notifying other military physicians about the effectiveness of this treatment.**
3. **Wide reporting of the study results at military and civilian medical conferences, newsletters, news releases, and journals.** It is the goal of the investigators to report the data from this study and the technique details in multiple forums. This will include presentations of abstracts at civilian and military medical conferences, as well as publication in journals such as Plastic and Reconstructive Surgery, Military Medicine, Orthopedic Trauma.
4. **Development of dedicated teaching tools and preceptor system to be made freely available to any surgeon.** This will be started during the early months of the study and completed by the end of the study. A teaching compendium will be produced that includes detailed technique description, case studies with photographs, and photographs and video segments that highlight technical details. Dr. Rubin has extensive experience publishing on surgical techniques and presenting surgical technical instructional courses. He understands that every case is an opportunity to collect and assemble teaching materials to assist other

surgeons. We will also work with the companies that make the equipment to have demonstration units available for teaching.

Another component of the teaching plan will be the establishment of a preceptor program open to surgeons who treat military trauma. Drs. Fleming and Valerio will welcome visiting surgeons to the operating room at the Walter Reed National Military Medical Center to observe cases.

Future Plans

WRNMMC / University of Pittsburgh

1. Continue to hold discussion with Renovacare to see if terms can be reached that would satisfy all parties while at the same time having the PIs pursue the use of an alternative technology. The Team plans to convene a discussion and make a decision as to the technology used once we are able to gather all the necessary information.
2. Identification of alternative technology that will meet the scientific requirements of this project.
3. Finalize overall study protocol, CRFs, informed consent which will serve as the basis for the University of Pittsburgh site-specific protocol and review by the University of Pittsburgh O3IS office.
4. Submit protocol, CRFs and informed consent to IRB.
5. Provide support for IDE preparation and submission by Pitt.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

There are no publications, abstracts, or presentations yet from this research.

INVENTIONS, PATENTS AND LICENSES:

There are no reportable inventions, patents or licenses to date from this research.

REPORTABLE OUTCOMES:

There are no reportable outcomes yet from this research.

OTHER ACHIEVEMENTS:

There are no reportable other achievements yet from this award.

REFERENCES:

There are no references included.

APPENDICES:

There are no appendices included.

AUTOLOGOUS SKIN CELL SPRAY FOR MASSIVE SOFT TISSUE WAR INJURIES:

A PROSPECTIVE, CASE-CONTROL, MULTI-CENTER TRIAL

Log OR110216

Organizational DUNS: 959131194

PI: CDR Mark E. Fleming, MC, USN

Org: Walter Reed National Military Medical Center

Award Amount: \$2,230,288.00



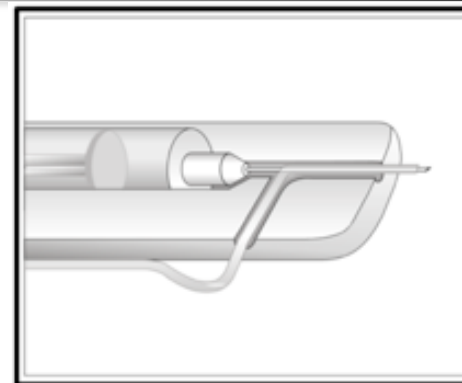
Study/Product Aim(s)

• **Treat extremity skin and soft tissue defects with an autologous skin cell spray transplantation in combination with dermal regenerative matrices (Integra).**

- 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), as well as healing on the cellular level (serial post-graft biopsies). Patients will be followed for 12 months after treatment to define long-term outcomes.

• **Assess the 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.



Using a linear motor that actuates the syringe plunger, the cell suspension flows slowly and constantly out of the syringe through a comparably large needle opening without pressure generation on the cells. Transferring the cell suspension out of a syringe through a needle into an air coat is as gentle to the cells as pipetting and thus avoids the cell injury associated with atomizers, but allows an even cell distribution over long periods of time in a continuous non pulsing stream.

Approach

Timeline and Cost

Activities	CY	13	14	15	16
Task #1 – Clinical Investigation & Cell Expansion (WRNMMC)					
Task #1A – External Site Clinical Investigation & Cell Expansion (UPitt)					
Task #2 – Data Management (University of Pittsburgh)					
Task #3 – Education and Training (WRNMMC)					
Estimated Budget (\$k)		\$791k	\$768k	\$546k	\$125k

Goals/Milestones

CY13/14 Goals – Regulatory

- ☐ Protocol Development; IDE & IRB approvals

CY14 Goals – Initiate Clinical Study including Cell Isolation and Expansion

- ☐ Initiate Recruitment of subjects

CY15 Goal – Continue & Complete Clinical Study including Cell Isolation and Expansion

- ☐ Recruitment subjects complete

CY16 Goal – Analysis/Data Preparation

Comments/Challenges/Issues/Concerns

- Significant delay in filing the IDE due to the time spent earlier in the process conducting the due diligence on the spray gun device & delay in receipt of device design history document needed for IDE application due to a conflict of interest

Budget Expenditure to Date

Projected Expenditure: 791k

Actual Expenditure: 367k

Updated: 15April2014