AWARD NUMBER: W81XWH-19-2-0017

TITLE: "A Randomized, Prospective, Within-Patient, Controlled Clinical Study to Investigate Full Thickness Skin Tissue Columns As a Novel Skin Replacement Therapy"

PRINCIPAL INVESTIGATOR: Rodney Chan, MD

CONTRACTING ORGANIZATION: The Metis Foundation
San Antonio, Texas 78205-1357

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

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"A Randomized, Prospective, Within-Patient, Controlled Clinical Study to Investigate Full Thickness Skin Tissue Columns As a Novel Skin Replacement Therapy"

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6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The Metis Foundation
300 Convent Street, Suite 1330
San Antonio, Texas 78205

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Split-thickness skin grafts (STSG), the current standard of care for wounds too large to heal effectively by linear closure, are typically harvested with a dermatome that TANGENTIALLY removes the epidermis and a thin layer of dermis from a donor site. Even though STSG have been the mainstay of skin replacement therapy since pinch grafts were described in 1869 by Reverdin, there are well-known limitations. In particular, STSG fail to adequately recapitulate some basic features of skin including pliability, uniform texture and color, and adnexal functions of lubrication and temperature regulation. Further, there is a finite number of possible re-harvests and donor sites from tangential harvests are not only painful (from exposure of nerve endings in the dermis) but also result in disfiguring scars in a previously uninjured region. Orthogonal skin harvest is a novel technique to obtain donor skin in the form of tissue columns for skin replacement therapy. The transfer of full thickness skin elements in columnar bits to a recipient wound bed may result in more functional skin and less donor site morbidity than conventional, tangentially-harvested, split thickness skin grafts. In this study, we propose to evaluate and compare tissue columns obtained from an FDA-cleared device, ART™ (Autologous Regeneration of Tissue), to split thickness skin grafts obtained from a conventional skin dermatome in a prospective, randomized, within patient, controlled study to determine quality and speed of healing as well as the need for re-grafting and donor site morbidity. The purpose of the study is to compare the efficacy and feasibility of skin harvest and replacement using: (1) Autologous Regeneration of Tissue (ART) device, which harvests FSTCs orthogonally to (2) conventional STSG harvested tangentially. The primary specific aim is to compare the quality of healing of the FSTC grafted recipient sites with the conventional STSG recipient sites. Secondary aims include evaluating the pain and healing of FSTC donor and recipient sites, the presence of adnexal structures and the need for reoperations for skin coverage.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified		**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

1. INTRODUCTION

Write a narrative (one paragraph) that describes the subject, purpose and scope of the research.

Orthogonal skin harvest is a novel technique to obtain donor skin in the form of tissue columns for skin replacement. The transfer of full-thickness skin elements in columnar bits to a recipient wound bed may result in more functional skin and less donor site morbidity than conventional, tangentially-harvested, split-thickness skin grafts. In this study, we propose to evaluate and compare tissue columns obtained from an FDA-cleared device, ART™(Autologous Regeneration of Tissue), to split-thickness skin grafts obtained from a conventional skin dermatome in a prospective, randomized, within-patient, controlled study to determine quality and speed of healing, as well as the need for re-grafting and donor site morbidity. The use of skin tissue columns as donor skin grafts presents a new paradigm for skin replacement, and this study is an important step to understanding how skin columns fit into our current surgical armamentarium for patients who have open wounds from surgery, trauma or burns.

2. KEYWORDS

Provide a brief list of keywords (limit to 20 words).

Orthogonal skin harvest; donor site morbidity reduction; skin tissue columns; skin replacement.

3. ACCOMPLISHMENTS

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project – (goals to be accomplished and status)

List the major goals of the project as stated in the approved Statement of Work (SOW). If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion. Only provide a STATUS update for either Major Task or Milestone Achieved for each Specific Aim.

Specific Aim 1 and 2: Obtain all necessary IRB approvals to conduct the proposed clinical trial.

Major Task 1: Prepare study protocol and associated regulatory documents for proposed study.
STATUS: COMPLETED, Y1Q1

Subtask 1: Coordinate with site for cooperative research and development agreement as needed (i.e. CRADA) for submission. Months 0-4.
STATUS: PENDING

Subtask 2: Coordinate with site for nondisclosure agreements (NDAs). Months 0-4
STATUS: COMPLETED, Y1Q1

Subtask 3: Submit study protocol (including: eligibility, screening protocol, consent forms etc.)
STATUS: IN PROGRESS, Y1Q2

Subtask 4: Military 2nd level IRB review (HRPO). Months 3-5
STATUS: PENDING

Subtask 5: Submit amendments, adverse events and protocol deviations. As needed.

STATUS: YET TO START

Subtask 6: Annual IRB/REB report for continuing review. Annually.
STATUS: YET TO START

Milestones Achieved: Local IRB/REB approval at MRDC IRB. Month 3.
STATUS: PENDING

Milestone Achieved: HRPO approval. Month 5.
STATUS: PENDING

Major Task 2: Patient screening and enrollment, treatment, sample collection and assessments
STATUS: YET TO START

Subtask 1: Subject recruitment. Months 6-18.
STATUS: YET TO START

Subtask 2: Subject screening and consent. Months 6-18.
STATUS: YET TO START

Subtask 3: Subject treatment. Months 6-18.
STATUS: YET TO START

Subtask 4: Subject follow-up visits; complete study measurements for study endpoints. Months 6-24
STATUS: YET TO START

Subtask 5: Enter and maintain all data in established database. Months 6-24.
STATUS: YET TO START

Subtask 9: Perform regular QA checks of database. Months 6-24.
STATUS: YET TO START

Milestone(s) Achieved: First subject recruited. Month 6.
STATUS: YET TO START

Milestone(s) Achieved: Last subject recruited. Month 18.
STATUS: YET TO START

Milestone(s) Achieved: Final sample and clinical data collection completed. Month 24.
STATUS: YET TO START

Major Task 3: Data analysis
STATUS: YET TO START

Subtask 1: Send stained tissue sections of biopsies to be graded by single blinded dermato-pathologist. Months 3-18.
STATUS: YET TO START

Subtask 3: Perform statistical analysis on all obtained data. Months 12-24.
STATUS: YET TO START

Milestone(s) Achieved: Complete analysis of all data. Months 24.
STATUS: YET TO START

Milestone(s) Achieved: Complete statistical analysis. Months 24.
STATUS: YET TO START

What was accomplished under these goals – (detailed progress and results)

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Task 1: Prepare study protocol and associated regulatory documents for proposed study.
The study protocol and supporting regulatory documents have been created for this project and submitted to the local IRB.

Subtask 1: Coordinate with site for cooperative research and development agreement as needed (i.e. CRADA) for submission. Months 0-4.
A master CRADA between the Metis Foundation and USAISR has been established. Currently the SOW and new requirement of a "Cooperative Agreement Letter (CAL)" have been drafted and are pending approval with the USAISR.

We are also working to establish proper agreements with Methodist hospital system to conduct the study at this site as well.

Subtask 2: Coordinate with site for nondisclosure agreements (NDAs). Months 0-4
The Metis Foundation master CRADA with the USAISR encompasses NDA.

Subtask 3: Submit study protocol (including: eligibility, screening protocol, consent forms etc.)
The study protocol and supporting regulatory documents have been withdrawn from the RHC-C IRB review. We will be submitting the protocol to MRDC and Methodist IRBs for approval at each prospective site.

What opportunities for training and professional development has the project provided?

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major

activities. If the project was not intended to provide training and professional development opportunities, or there is nothing significant to report during this reporting period, state "Not applicable" or "Nothing to report."

Nothing to report.

How were the results disseminated to communities of interest?

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities. Also, if applicable, you may simply state, "See publications and/or presentations." If there is nothing significant to report during this reporting period, state "Nothing to report."

Nothing to report.

Plans for the next reporting period to accomplish the goals

Describe briefly what you plan to do during the next reporting period to accomplish the remaining goals and objectives. If this is the final technical report, state "Work is completed."

Next reporting period plans consist of obtaining details of the FDA approval to utilize the device in this study and obtain approved device from the sponsor, Medline. We also will be working towards obtaining local IRB and HRPO approval of the study protocol.

4. IMPACT

Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style). If there is nothing significant to report during this reporting period, state "Nothing to report."

Nothing to report.

What was the impact on other disciplines?

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines. If there is nothing significant to report during this reporting period, state "Nothing to report."

Nothing to report.

What was the impact on technology transfer?

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including: 1) transfer of results to entities in government or industry; 2)

instances where the research has led to the initiation of a start-up company; or 3) adoption of new practices, etc. If there is nothing significant to report during this reporting period, state "Nothing to report."

Nothing to report.

What was the impact on society beyond science and technology?

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as: 1) improving public knowledge, attitudes, skills, and abilities; 2) changing behavior, practices, decision making, policies (including regulatory policies), or social actions; 3) improving social, economic, civic, or environmental conditions, etc. If there is nothing significant to report during this reporting period, state "Nothing to report."

Nothing to report.

5. CHANGES/PROBLEMS

The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Contracting/Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information.

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. If there is nothing significant to report during this reporting period, state "Nothing to report."

On 03 June 2020, an amendment to the SOW was submitted to include an additional site, Methodist hospital. Due to delays with FDA and device manufacturer, we have requested to add an additional site to increase potential enrollment once approved utilizing same research staff at both sites.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them. Also report any actual or anticipated financial or contracting matters in addition to technical challenges that may impact the project's performance or progress. If there is nothing significant to report during this reporting period, state "Nothing to report."

The manufacturer, Medline, is currently conducting the design verification and validation activities, with anticipated completion in Q4 2020. Manufacturing for human-use product can't be initiated until testing is completed. Medline continues communications with FDA in regards approval and DeNovo clearance; next FDA teleconference is scheduled for August.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated. If there is nothing significant to report during this reporting period, state "Nothing to report."

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the approval dates, including continuing reviews or renewals, and/or amendments for animal use and/or human subject research protocol(s) for each regulatory reviews, i.e. the Institutional Animal Care and Use Committee (IACUC) and the DoD Animal Care and Use Review Office (ACURO), and the Institutional Review Board (IRB) and the DoD Human Research Protection Office (HRPO).

Significant changes in use or care of human subjects

Replace prompt and write per instructions above in this self-expanding table cell, or if there is no human subject research involved write "Not applicable" and remove the below information requested. Otherwise complete the format below for each protocol (if necessary, copy and paste the below format for each additional protocol):

IRB Protocol Number: Pending
HRPO Protocol Number: Pending assignment
Protocol PI: Rodney K. Chan, MD
Site: US Army Institute of Surgical Research Burn Center and San Antonio Methodist Hospital System
Title: Full-Thickness Microscopic Skin Tissue Column Grafting Technique Using the ART (Autologous Regeneration Tissue) System: An Interventional Clinical Trial
Target required for clinical significance: 40
Target approved for clinical significance: Pending

Significant changes in use or care of vertebrate animals

Replace prompt and write per instructions above in this self-expanding table cell, or if there is no animal use research involved write "Not applicable" and remove the below information requested. Otherwise complete the format below for each protocol (if necessary, copy and paste the below format for each additional protocol):

- Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS

List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Publications, conference papers, and presentations

Report only the major publication(s) resulting from the work under this award.

Journal publications
List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Follow the format:

1. Authors names in format of Last Name First Initial followed by comma for each additional names (use et al if more than 10 authors). Title of paper. Journal Name Abbreviated Form. Year Month Date; Volume (Issue#):page numbers. doi: #. PubMed PMID: #; PubMed Central PMCID: #
    a. List publication type (e.g. original manuscript, review, abstract, etc.)
    b. State publication status (e.g. submitted, under review, accepted, or published)
    c. Reference which specific aim (e.g. Directly related to SOW, specific aim 1)
    d. State award funding acknowledgement (e.g. DoD funding acknowledged)

Nothing to report.

Books or other non-periodical, one-time publications
Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like.
Follow the format:

1. Authors names in format of Last Name First Initial followed by comma for each additional names (use et al if more than 10 authors). Chapter title if applicable. Title of the book. Edition. Publication. Publication date. (Chapter, page info if applicable). ISBN/doi: / PMID.
    a. List publication type (e.g. book, dissertation, conference proceedings, supplemental, etc.)
    b. State publication status (e.g. submitted, under review, accepted, or published)
    c. Reference which specific aim (e.g. Directly related to SOW, specific aim 1)
    d. State award funding acknowledgement (e.g. DoD funding acknowledged)

Nothing to report.

Other publications, conference papers, and presentations
Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made, including international, national, local societies, military meetings, etc. Use an asterisk (*) if presentation produced a manuscript.
Follow the format:

1. Authors names in format of Last Name First Initial followed by comma for each additional names (use et al if more than 10 authors), Speaker*. Month. Year. Title. Name of Meeting, Location of Meeting
    a. List presentation type (e.g. invited, talk, poster, or government review, etc.)
    b. State presentation status (e.g. submitted, under review, accepted, or presented)
    c. Reference which specific aim (e.g. Directly related to SOW, specific aim 1)
    d. State award funding acknowledgement (e.g. DoD funding acknowledged)

Nothing to report.

Website(s) or other Internet site(s)
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

Technologies or techniques

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report.

Inventions, patent applications, and/or licenses

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award. Follow the format:

1. Inventors names in format of Last Name First Initial followed by comma for each additional names (use et al if more than 10 authors). Year. Title. US Patent No.
    a. List patent type (e.g. provisional, international, etc.)
    b. State patent status (e.g. filed, issued)
    c. Reference which specific aim (e.g. Directly related to SOW, specific aim 1)
    d. Anything else (e.g. filed before award)

Nothing to report.

Other Products

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include: 1) data or databases; 2) biospecimen collections; 3) audio or video products; 4) software; 5) models; 6) educational aids or curricula; 7) instruments or equipment; 8) research material (e.g., Germplasm, cell lines, DNA probes, animal models); 9) clinical interventions; 10) new business creation; etc.

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Report PDs/PIs and for each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Replace prompt and write per instructions above in this self-expanding table cell using the format/table below for each person (if necessary, copy and paste the below format/table for each additional person):

Name:	Rodney K. Chan
Project Role:	PI
Researcher Identifier:	
Nearest person month worked:	12 months
Contribution to Project:	Dr. Chan has performed work in the area overall oversight of study design, preparation and progress.

Name:	Victoria D. Hatem
Project Role:	Research Coordinator
Researcher Identifier:	None
Nearest person month worked:	12 months
Contribution to Project:	Ms. Hatem has performed work in the area of protocol design, regulatory preparation, IRB submission and communications and preparation of study agreements.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Follow the format:

Organization Name:
Location of Organization: (if foreign location list country)
Partner's Contribution to the Project: (identify one or more, e.g. 1) financial support; 2) in-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff); 3) facilities

(e.g., project staff use the partner's facilities for project activities); 4) collaboration (e.g., partner's staff work with project staff on the project); 5) personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); etc.

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS

For collaborative awards, independent reports are required from both the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site.

QUAD CHART

Insert an updated Quad Chart as one of the appendices (best to convert this technical report in Word file and the quad chart in PowerPoint file into separate PDF files, and then assemble into a single PDF document for submission via eBRAP).

9. 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, and surveys, etc.