AWARD NUMBER: W81XWH-17-2-0061

TITLE: Implantation of full-thickness skin columns to decrease hypertrophic scar formation after deep partial thickness burns

PRINCIPAL INVESTIGATOR: Rodney Chan, MD

CONTRACTING ORGANIZATION: Metis Foundation San Antonio, TX 78205-1357

REPORT DATE: October 2019

TYPE OF REPORT: ANNUAL

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

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14. ABSTRACT							
PURPOSE: The	purpose of this stu	dy is to provide pro	pof-of-concept, pre	-clinical evid	ence for use of autologous full-		
thickness skin col	umn implantation	for the treatment of	f deep partial-thick	ness burn inji	ury to prevent hypertrophic scar		
formation. This e	vidence will suppo	ort a pivot into clini	cal trials of this stra	ategy.	-		
OBJECTIVES:	The long-term obj	ective is to develop	autologous full-th	ickness skin c	column implantation as an		
improved low-me	arhidity methodole	ov for the treatment	t of deen nartial th	ickness hurn	The scientific objective of this		
proposal is to arr	luoto the contraction	onithelialization	and late (next an: 1)	alialization	officially of three different condin-		
proposal is to eva	inate the early (pro	e-epimenanzation)	and fate (post-epitr	ienanzation)	enicacy of three different seeding		
ratios of <i>implante</i>	d full-thickness sk	in columns in redu	cing hypertrophic s	scar formation	n by accelerating wound closure,		
improving skin quality parameters, reducing wound contraction and minimizing donor-site morbidity in a porcine model							
of deep partial thickness burn.							
15. SUBJECT TERMS							
Burn wound hea	aling, skin gra	aft, skin repla	cement therapy,	, skin subs	stitute		
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1. INTRODUCTION:

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

SINGLE HYPOTHESIS: Autologous full-thickness skin columns implanted into the residual dermis of debrided deep partial-thickness burns will decrease hypertrophic scar formation with minimal donor site morbidity.

PURPOSE: The purpose of this study is to provide proof-of-concept, pre-clinical evidence for use of autologous full-thickness skin column implantation for the treatment of deep partial-thickness burn injury to prevent hypertrophic scar formation. This evidence will support a pivot into clinical trials of this strategy.

OBJECTIVES: The long-term objective is to develop autologous full-thickness skin column implantation as an *improved, low-morbidity* methodology for the treatment of deep partial-thickness burn. The scientific objective of this proposal is to evaluate the early (pre-epithelialization) and late (post-epithelialization) efficacy of three different seeding ratios of *implanted* full-thickness skin columns in reducing hypertrophic scar formation by accelerating wound closure, improving skin quality parameters, reducing wound contraction and minimizing donor-site morbidity in a porcine model of deep partial thickness burn.

PREDICTED OUTCOME: The predicted outcome of this study is the identification of an optimal seeding ratio for full-thickness skin column treatment of deep partial thickness burn and the development

2. KEYWORDS:

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

Burn wound healing, skin graft, skin replacement therapy, skin substitute

3. ACCOMPLISHMENTS:

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

What were the major goals of the project?

List the major goals of the project as stated in the approved 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. *Red percentages/text represent updated cumulative progress under FY19.

Specific Aim 1: Identify optimal implanted FTSC seeding density and treatment	Timeline	%
modality for early treatment of open, debrided deep partial-thickness burn	Months	completed
Subtask 1: Obtain approval of local IACUC for porcine study	0-2	100%
Subtask 2: Obtain 2 nd level ACURO approval	2-3	100%
Subtask 3: Perform animal studies for Aim 1a: Optimization of FTSC seeding	2.0	1000/
density for early treatment of deep partial-thickness burn.	3-9	100%
Subtask 4: Perform analysis of primary endpoint for Aim 1a	9-12	100%
Subtask 5: Perform analysis of secondary endpoints for Aim 1a	9-12	100%
Milestones Achieved: Local IACUC approval at USAISR	2	100%
Milestone Achieved: ACURO approval	3	100%
Milestone Achieved: Optimized seeding ratio for early implantation	9-12	100%
Subtask 1: Perform animal studies for Aim 1b: Comparative evaluation of early	10.16	1000/
treatment of deep partial-thickness burn with implanted versus topical FTSCs	12-10	100%
Subtask 2: Perform analysis of primary endpoint for Aim 1b	16-19	80%
Subtask 3: Perform analysis of secondary endpoints for Aim 1b	16-19	80%
Subtask 4: Perform animal studies for Aim 2: Identify optimal implanted FTSC	19.20	1000/
seeding density for late treatment of epithelialized deep partial-thickness burn	18-20	100%
Subtask 5: Perform analysis of primary endpoint for Aim 2	20-22	30%
Subtask 6: Perform analysis of secondary endpoint for Aim 1b	20-22	30%
Milestone(s) Achieved: Question of topical vs. anatomic implantation	16-19	40%
Milestone(s) Achieved: Optimized seeding ratio for late implantation	22-24	

Subtask 1: Perform animal studies for Aim 3: Determine donor skin quality after FTSC harvests	3-9	15%
Subtask 2: Perform analysis of primary endpoint for Aim 3	9-12	
Subtask 3: Perform analysis of secondary endpoints for Aim 3	9-12	
Milestone(s) Achieved: donor skin quality of FTSC harvests	9-12	
Milestone(s) Achieved: Complete statistical analysis of all data (Aims 1-3)	19-24	

What was accomplished under these goals?

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.

- 1) Major activities
 - Aim 1b analysis and Aim2 porcine experiments.
- 2) Specific objectives Analyzing FTSC implantation vs topical FTSC under Aim 1b and conducting Aim 2 animal experiments.
- 3) Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or

Porcine FTSC implantation have successfully been implanted under aim 1a. Figure 1 shows skin column progress over 90 days for all skin column ratios.



Epithelialization

Figure 1. Show graphs using preliminary datasets of Re-epithelialization, perfusion and percent contraction. Reepithelialization of wounds was faster in the 1:1 and 1:2 groups while the 1:4 and 1:9 ratios performed about as fast as the untreated control. Perfusion data show a slightly faster healing profile in the 1:1 and 1:2 ratio groups during day 7-28. There is no difference in the perfusion data set after day 28. The 1:1 and 1:2 ratio groups exhibited the least amount of contraction. 1:4 and 1:9 groups didn't show any improvement as compared to the untreated burn wound.

Full-Thickness Skin Columns in the Treatment of Deep Partial Thickness Burns

David H. Tassin, MD, Timothy C. Haire, PhD, Anders H. Carlsson, PhD, Tyler R. Everett, MLT, Javier A. Chapa, B.S.,

Rodney K. Chan, MD US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX





Figure 2. Preliminary data presented on poster during ABA2019.

Summary: Aim 1a, 1b and 2 animal experiments have progressed well. We're assessing/analyzing data and histology acquired during aim 1 and aim 2 experiments. In this quarterly report we show histology from both implanted skin columns and donor sites. We also show early data on re-epithelialization, laser speckle perfusion and contraction.

4 Other achievements. Include a discussion of stated goals not met.

Analysis of Aim 1 and execution of Aim2 experiments have progressed well despite some issues with core facilities and contracting. The main issues during this year have been:

(1) Delays in histology processing and analysis due to histology core renovations. The Histo facilities are now renovated and the personnel are catching up on the work log.

(2) Delay in getting the intended pig breed for our experiments. The ISR vivarium has been working on setting up a contract to receive red Duroc and Duroc hybrids from additional vendors that fulfill needed lab animal standards. The contract is almost finalized as on Oct 2019.

(3) ISR internal software for placing work orders (Research Management System – RMS) is currently undergoing an update at the end of the fiscal year. The update is taking longer than intended and no new pig orders or work orders for histology can be placed or processed until the software is updated.

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

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 "Nothing to Report."

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.

This project allows for several opportunities of training and professional development. Most opportunities are in smaller study groups or at the individual level. Examples of training opportunities for residents, post-docs and techs include; 1) Animal ethics & porcine animal studies, 2) Porcine pain assessments and pain management in research animals, 3) Porcine burns and how to conduct dressing changes, wound & scar assessments etc. 4) The importance of adherence and maintenance of IACUC/ACURO protocols. 5) Opportunities to present data (Posters and oral presentations) at conferences.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

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.

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals? *If this is the final report, state "Nothing to Report."*

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

The main focus will be on analyzing data from Aim 2 (**Identify optimal implanted FTSC seeding density for late treatment of epithelialized deep partial-thickness burn**) and conducting Aim 3 (**Determine donor skin quality after FTSC harvests**).

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?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

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).

Nothing to Report

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

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.

Nothing to Report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

• transfer of results to entities in government or industry;

• *instances where the research has led to the initiation of a start-up company; or adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

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:

- *improving public knowledge, attitudes, skills, and abilities;*
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. CHANGES/PROBLEMS:

The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Approved No cost extension. We have received an approved no cost extension of the performance period of this project. The SOW remains the same – no changes has been done to the project or it's direction.

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.

- 1. Long wait for histopathologic assessment/scoring. The renovations of the core histology laboratory have delayed processing and analysis of our samples. Although the renovations are complete the core histology laboratory is now working on the backlog resulting in that the turnaround time for the ISR core histopathology assessments is very slow. The core lab should soon be all caught up and our samples processed faster. (- see previous quarterly report for details)
- 2. Shortage of red Duroc and Duroc hybrid with ISR porcine vendor. The ISR vivarium vendor for red Duroc and purebred Durocs have not had sufficient supply of Durocs. A new contract have been initiated and is close to finalized. The new vendor should be able to provide a sufficient number of Durocs that adhere to the ISR vivarium quality standards.
- 3. Delayed software update of the Research Management System, RMS. A planned update to RMS was intended to be performed at the end of the 2019 fiscal year. The update is taking longer than anticipated and is still not completed. As RMS is used to order animals and for orders on core services this has incurred some delay in our progress. However, since this coincides with the new pig vendor contract (Described above) there is no additional delay. Updates should be completed before the end of October.

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.

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 applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report –N/A

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report –N/A

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. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report -Yet

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. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

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 during the last year (international, national, local societies, military meetings, etc.).* Use an asterisk (*) if presentation produced a manuscript.

Presented at ABA 2019, Las Vegas.

• 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. Describe the technologies or techniques were 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. 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.

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:

- data or databases;
- physical collections;
- audio or video products;
- software;
- models;
- educational aids or curricula;
- *instruments or equipment;*
- research material (e.g., Germplasm; cell lines, DNA probes, animal models);
- *clinical interventions;*
- new business creation; and
- other.

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) 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".

<u>Example:</u>	
Name:	Mary Smith
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	1234567
Nearest person month worked:	5
Contribution to Project:	Ms. Smith has performed work in the area of combined error-
	control and constrained coding.
Funding Support:	The Ford Foundation (Complete only if the funding
	support is provided from other than this award.)

Name:	Rodney Chan, MD.
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	<u>https://orcid.org/0000-0002-5061-847X</u> https://scholar.google.com/citations?user=Cu787kYAAAAJ&hl=sv
Nearest person month worked:	4
Contribution to Project:	Dr. Chan is the PI of the award.
Funding Support:	The Metis Foundation
Name:	Anders Carlsson, PhD.
Project Role:	Co-Principal Investigator
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-4846-108X https://scholar.google.com/citations?user=WdVK3Z8AAAAJ
Nearest person month worked:	10
Contribution to Project:	Dr. Carlsson is the Co-PI of the award.
Funding Support:	The Metis Foundation

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 there is nothing significant to report during this reporting period, state "Nothing to Report."

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?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

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.

Provide the following information for each partnership: <u>Organization Name:</u> <u>Location of Organization: (if foreign location list country)</u> <u>Partner's contribution to the project</u> (identify one or more)

- Financial support;
- In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
- Facilities (e.g., project staff use the partner's facilities for project activities);
- Collaboration (e.g., partner's staff work with project staff on the project);
- Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and
- Other.

<u>Organization Name:</u> The Metis Foundation <u>Location of Organization:</u> 300 Convent Street, Suite 1330. San Antonio, TX 78205 <u>Partner's contribution to the project</u>: In-kind support, Collaboration, Personnel exchanges

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <u>https://ers.amedd.army.mil</u> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <u>https://www.usamraa.army.mil</u>) should be updated and submitted with attachments.

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.

Full thickness Skin Columns (FTSC) Implantation to Decrease Hypertrophic Scar after Partial-Thickness Burn

W81XWH-17-2-0061

epithelialization.

following DPTB.

establish mechanism of action

PI: Rodney Chan, MD/Anders Carlsson, PhD Org: Metis Foundation/USAISR

Study/Product Aim(s) Study Goal: Accelerate wound closure and improve regenerated skin quality using FTSC implantation after deep-partial thickness burn (DPTB).

AIM 2: Establish optimal late FTSC seeding density for treatment of DPTB. This aim will simulate the treatment of burns after re-epithelialization.

Approach

Using established porcine models of DPTB we will compare wound

kinetics, restoration integumentary function and regenerated skin quality after treatment with or without implanted FTSC. Treatment strategies will include three different ratios of FTSCs implantation in residual dermis

hypertrophy, transepidermal water loss and patient observer scar scale

(POSAS). Histopathology and expression analysis will be investigated to

AIM 1: Establish optimal early FTSC seeding density for treatment of DPTB. This aim will simulate the treatment of acute burns before reAward Amount: \$615,969



A) visualize the skin column implantation/technique. B) Shows a close up on a debrided partial-thickness burn after implantation of skin columns. C) Shows the skin column donor site on the shoulder/neck portion of the animal.

Goals/Milestones

FY18 Goal - Begin FTSC seeding studies in DPTB.

- ✓ Obtain IACUC approval for and validate DPTB models
- Validate FTSC harvest technique and device \checkmark
- ✓ Finalize protocol for FTSC treatment of DPTB
- Begin AIM 1, early treatment of DPTB seeding density experiments \checkmark
- ✓ Begin AIM 2, late treatment of DPTB seeding density experiments

FY19 Goals - Complete DPTB experiments, data collection/analysis, publish and close-out.

- ✓ Complete AIM 1, early treatment experiments
- ✓ Complete AIM 2, late treatment experiments
- Complete data collection/analysis for AIM 1 and AIM 2 data.

Comments/Challenges/Issues/Concerns: Delays due to ISR histology core renovations and new pig vendor contract.

Budget Expenditure to Date: September 30, 2017 – October 22, 2019 Projected Expenditure Years 01-02: \$615,969.00 \$420,899.77 Actual Expenditure:

Timeline and Cost

AIM	TASKS AND MILESTONES	FY	18	19
	Regulatory approvals (IACUC)			
1	Evaluate FTSC treatment of DPTB Establish seeding density for early FTSC treatment	nent		
2	Evaluate FTSC treatment of DPTB - 2a: seeding density for late FTSC treatment			
3	Data analysis, review, publication			
4	Study close-out			
Propos	al Budget (\$K) TOTAL: \$615		\$312.5	\$303.4

Updated: October 22, 2019