

AWARD NUMBER: W81XWH-17-1-0287

TITLE: Multi-parametric Bioreactor for Functional Preservation of Vascularized Composite Allografts

PRINCIPAL INVESTIGATOR: Gerald Brandacher, MD

RECIPIENT: Johns Hopkins University

REPORT DATE: OCTOBER 2020

TYPE OF REPORT: Annual Report

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

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14. ABSTRACT 1. More than half of the combat-related injuries per peer reviewed analyses of the Joint Theater Trauma Registry sustained by Warfighters in Iraq and Afghanistan involved extremities or craniofacial structures. An estimated 40% of all combat casualties in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) resulted in injuries to the extremities, face, and head and neck structures. Vascularized composite allotransplantation has increasingly become a viable clinical treatment option for the treatment of complex craniofacial and limb defects. To date, more than 100 patients worldwide have benefited from VCA, the majority receiving hand or face transplants. However, the transformational potential of VCA is severely limited by short preservation times (4 – 6 hours) 2. This work will deliver ex vivo VCA perfusion technology intended to extend preservation time to 24 hours and minimize ischemia damage by efficient perfusion and multi-parametric monitoring.					
15. SUBJECT TERMS VCA preservation, electrical stimulation, biosensor					
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Background. More than half of the combat-related injuries per peer reviewed analyses of the Joint Theater Trauma Registry sustained by Warfighters in Iraq and Afghanistan involved extremities or craniofacial structures. An estimated 40% of all combat casualties in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) resulted in injuries to the extremities, face, and head and neck structures. Vascularized composite allotransplantation has increasingly become a viable clinical treatment option for the treatment of complex craniofacial and limb defects. To date, more than 100 patients worldwide have benefited from VCA, the majority receiving hand or face transplants. However, the transformational potential of VCA is severely limited by short preservation times (4 – 6 hours) and all the logistical difficulties that come with this limitation. VCA survival is highly dependent on the ischemia injury happening during preservation. Consequently, organ preservation plays a major role in improving the clinical outcome of transplantation. Extracorporeal perfusion systems have demonstrated superior preservation outcome in different solid organs comparing to cold storage. Therefore there is critical need for developing preservation technology based on ex-vivo perfusion to enhance VCA preservation.

Objective/Hypothesis. This work will deliver ex vivo VCA perfusion technology intended to extend preservation time to 24 hours and minimize ischemia damage by efficient perfusion and multi-parametric monitoring.

Specific Aims.

Specific Aim 1. Engineer multi-parametric bioreactor system designed for preservation and real-time monitoring of NO/ROS in rat abdominal wall VCA. We designed stand-alone perfusion/electrical stimulation system maintaining viability of rat abdominal wall.

Specific Aim 2. Preserve viability and function of abdominal wall VCA up to 72 hours in bioreactor and establish the viability biomarker profile. We will develop ES protocol to enhance abdominal wall VCA preservation.

Specific Aim 3. Preserve whole extremity VCA in bioreactor and assess post-transplant viability and function. A new multi-parametric bioreactor will be designed based on the knowledge of bioreactor design we gain from the first aim and will preserve rat forelimb VCA for longer than 24 hours.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Vascularized composite allograft, ex-vivo perfusion, biosensor, electrical stimulation, rat abdominal wall

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? *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.*

Specific Aim 1	Timeline	Progress
Major Task 1: Engineer multi-parametric bioreactor system designed for preservation and real-time monitoring of NO/ROS in rat abdominal wall VCA.	Months	
Task 1A: Design stand-alone perfusion/electrical stimulation system maintaining viability of rat abdominal wall	1-12	100%
Task 1B: Develop in-line sensors to measure concentrations of NO and ROS for non-invasive, real-time graft monitoring.	1-18	85%
Milestone(s) Achieved: ACURO approval for studies in Aims 2 & 3.		
Specific Aim 2		
Major Task 2: Preserve viability and function of abdominal wall VCA up to 72 hours in bioreactor and establish the viability biomarker profile.		
Task 2A: Optimize ES protocol to enhance abdominal wall VCA preservation.	6-18	80%
Task 2B: Preserve abdominal wall VCA for up to 72 hours through perfusion and ES. Utilize non-invasive measurements to establish a 'viability biomarker profile' and correlate with post-transplant viability.	6 – 24	70%
Milestone(s) Achieved:		
Specific Aim 3		
Major Task 3: Preserve whole extremity VCA in bioreactor and assess post-transplant viability and function.		
Task 3A: Re-design multi-parametric bioreactor to provide ES of the flexor and extensors forearm muscles of the rodent upper extremity transplant.	18 – 24	0%
Task 3B: Preserve rat forelimb VCA in bioreactor for 24 – 72 hours post-procurement. Assess ischemia-reperfusion injury, graft viability, and long-term function following bioreactor preservation.	18 - 36	0%
Milestone(s) Achieved:		

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.

Major activities:

Task 1A: Design stand-alone perfusion/electrical stimulation system maintaining viability of rat abdominal wall

We have developed sub-normothermic ex-vivo perfusion and incorporated electrical stimulation with real-time monitoring systems capable of stimulating muscle of rat abdominal wall and measuring contraction force, perfusion pressure, pH, oxygen, and temperature.

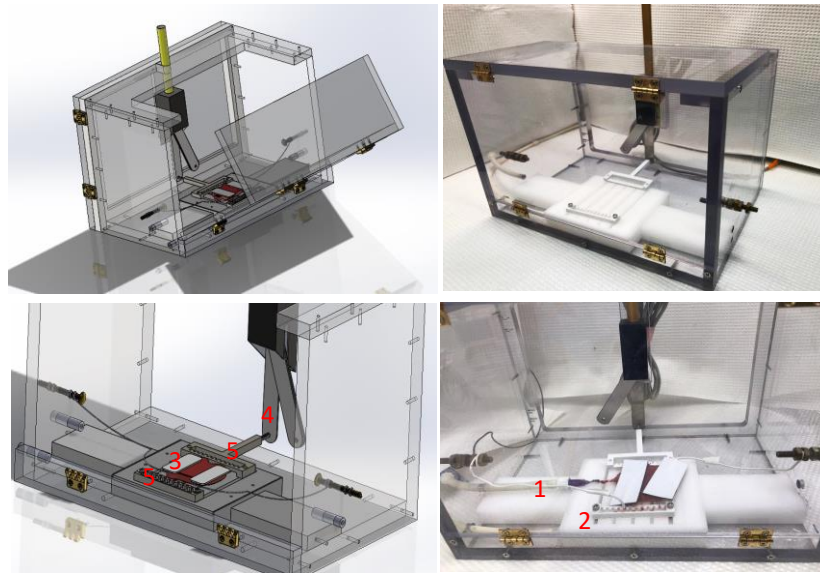


Figure 1. Custom-designed bioreactor for housing of rat abdominal wall connected to ex-vivo perfusion and electrical stimulation systems. 1. Ex-vivo perfusion inlet 2. Collecting reservoir (perfusion outlet) 3. Electrodes 4. Force sensor 5. Clamps

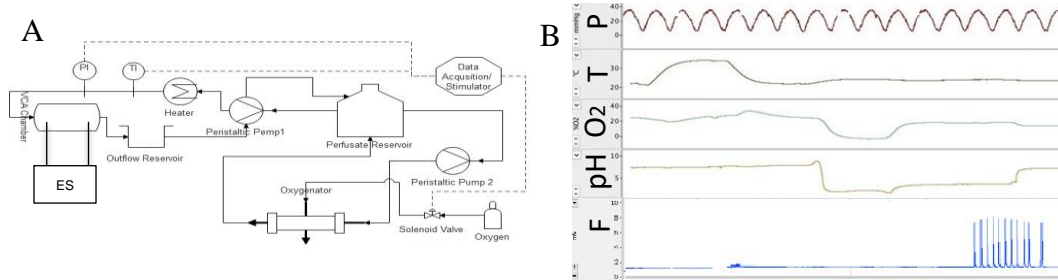


Figure 2. A. Process Flow Diagram of sub-normothermic ex-vivo perfusion system B. Read-out of real-time monitoring system after disturbance in perfusion's parameters

Subtask 2.A: Optimize ES protocol to enhance abdominal wall VCA preservation.

To optimize electrical stimulation protocol that improves perfusion and reduces perfusion-induced damage in abdominal wall, a pilot study has been conducted. The pilot study was aimed at testing the single contraction electrical stimulation protocol which has been widely studied in contraction-induced vasodilation research studies. We hypothesized that muscle stimulation causing contraction dilates the vessels and improves perfusion which leads to less tissue swelling. Three euthanasia rats were used. Abdominal wall was perfused for 12 hours and graft was stimulated after blood removal which is 30 minutes into perfusion. Perfusion pressure exhibited drop after three single contractions which had not happened in previous perfused grafts. Perfusion pressure drop is shown in Figure 3C.

However, the euthanasia rats were more than one year old. Aged rats have shown higher arterial pressure. we speculate that might be the reason that we observed slightly higher perfusion pressure in the pilot study outcome. The drop we observed in the pressure is promising to conduct a controlled study testing this hypothesis. Experimental plan is depicted in Figure 4.

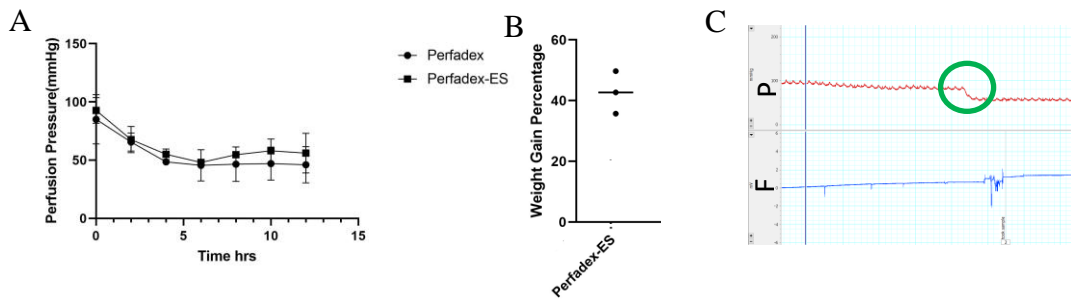


Figure 3. Impact of electrical stimulation at the beginning of 12-hour perfusion on abdominal wall. A. Perfusion pressure B. Grafts' weight gain at the end of perfusion C. Pressure and force sensor read-out showing drop in perfusion pressure shortly after three single contractions

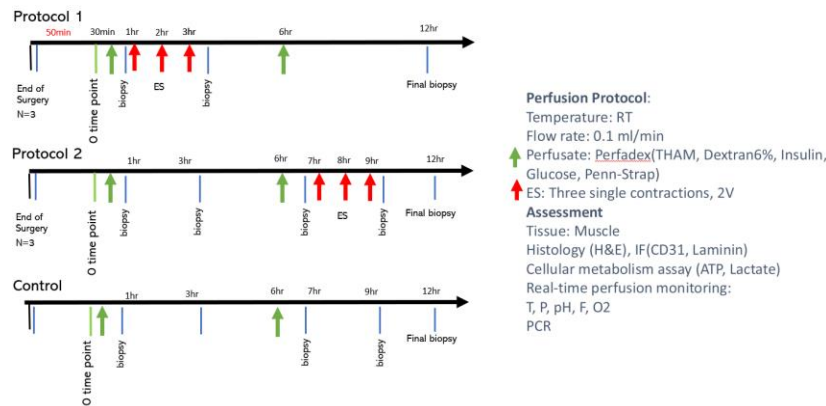


Figure 4. Controlled study to test ES impact on abdominal wall ex-vivo perfusion

Subtask 2.B: Preserve abdominal wall VCA for up to 72 hours through perfusion and ES. Utilize non-invasive measurements to establish a 'viability biomarker profile' and correlate with post-transplant viability

Preserving abdominal wall for up to 72 hours requires finishing several important steps described as follows.

Animal Model

Rat abdominal wall model had been developed in Dr. Brandacher's lab and used for research on transplantation (Figure 5). We have modified the graft to become suitable for extended ex-vivo perfusion and demonstrated that it is perfusable by perfusing Evans blue dye at the beginning and at the end of 12-hour machine perfusion (see Figure 6). The investigation on animal model and following research on development of ex-vivo perfusion protocol has been done with euthanasia rats.

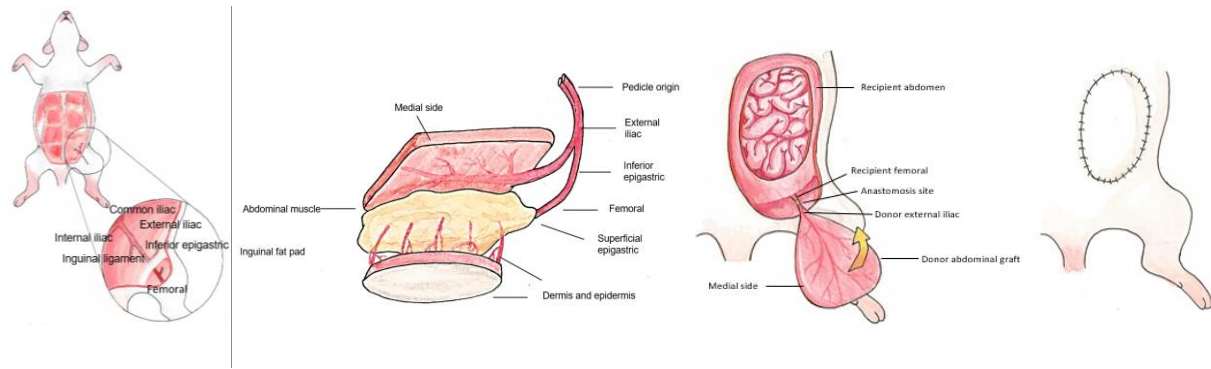


Figure 5. Illustration of rat abdominal wall animal model for VCA studies. A. Vessels perfusing abdominal wall B. Tissue layers and vessels perfusion the graft C. Abdominal wall graft after anastomosis of recipient's femoral artery D. Transplantation of abdominal wall

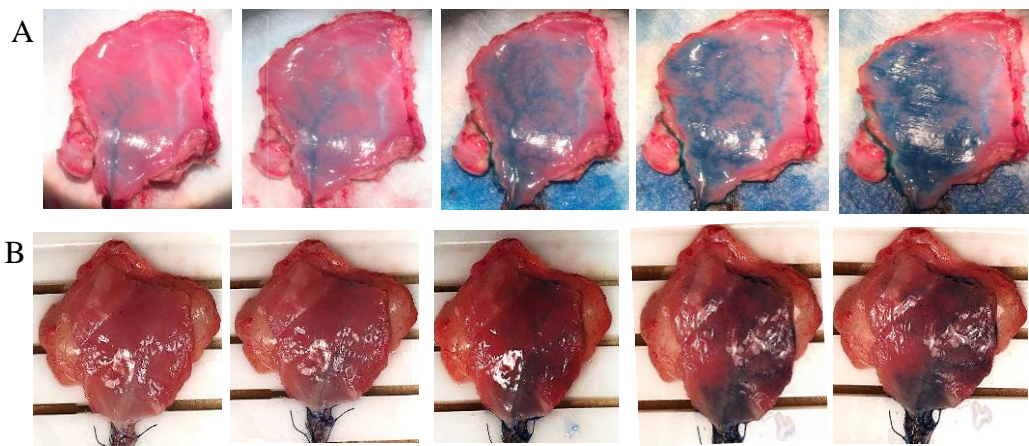


Figure 6. Evans blue dye perfusion at the beginning (A) and at the end (B) of 12-hour perfusion demonstrating that the graft is perfusable. Images were taken at 10-minute interval

Control group (cold storage and transplantation)

Our proposed multi-parametric bioreactor is being developed as an alternative to current gold standard in organ preservation, therefore, its accuracy needs to be investigated against cold storage. We have studied cutoff time for cold storage to use as control group for later studies. After 24 and 48 hours of cold storage abdominal wall have been transplanted to recipients(n=2). This study has been done with 8-week Lewis rats per ACURO protocol. Grafts preserved for 48 hours did not survive more than 3 days of post transplantation.

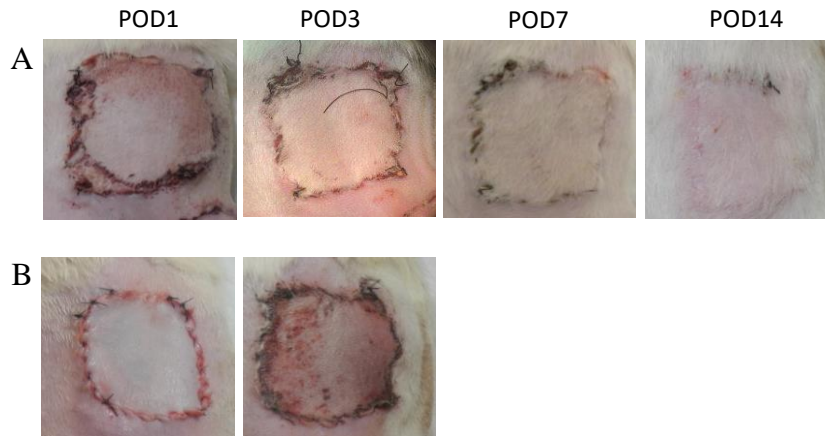


Figure 7. Representative images post transplantation follow-up of grafts preserved by cold storage for A. 24 hours and B. 48 hours.

Perfusate

Extended machine perfusion demands a base perfusate delivering required electrolytes and osmotic pressure to minimize tissue swelling. We have investigated commercial preservation solutions (HTK vs Perfadex) and colloids (Dextran vs Albumin) to find the optimum base perfusate. Figure 8 shows viability and tissue swelling after 12 hours of perfusion in which Perfadex demonstrates the best outcome among other perfusates.

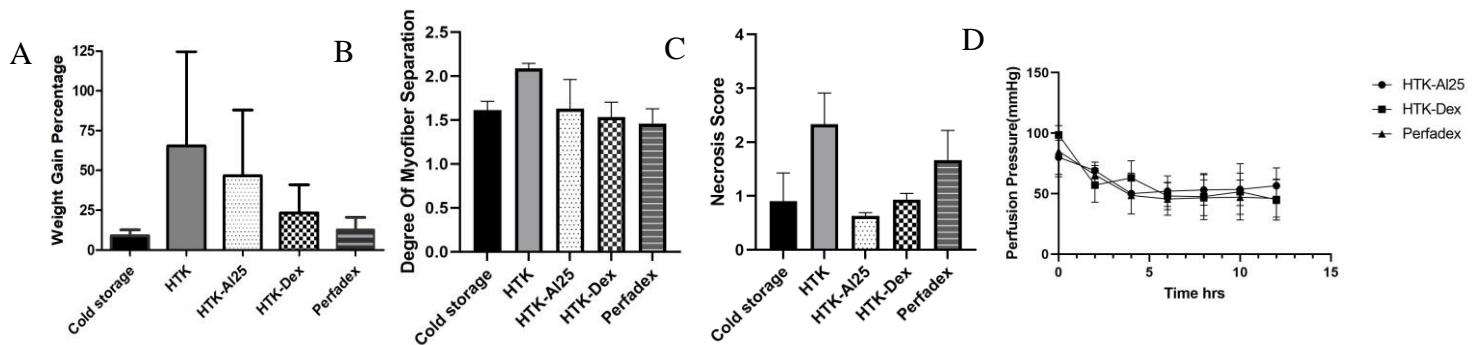


Figure 8. Histology result and perfusion pressure of grafts perfused by HTK, HTK-Albumin 25%, HTK-Dextran and Perfadex in comparison with grafts preserved by cold storage for 12 hours.

Oxygenation

In extended sub-normothermic machine perfusion oxygenation is critical to support cellular metabolism. Two methods have been studied; first is oxygenating perfusate without any oxygen carrier and second is oxygenation with an oxygen carrier, natural or synthetic. The first method cannot provide enough oxygenation to cells at close-to-normal temperature. We have studied using red blood cell (natural) and hemoglobin-based oxygen carrier (synthetic). Figure 9 demonstrates result of pilot studies with the oxygen carriers. Implementing oxygenation by using red blood cells gives rise to several technical challenges and the un-modified

hemoglobin-based oxygen carrier exhibited significant infiltration to interstitial space. Therefore, we have planned to study modified hemoglobin-based oxygen carrier which has shown minimum injury to tissue in next study.

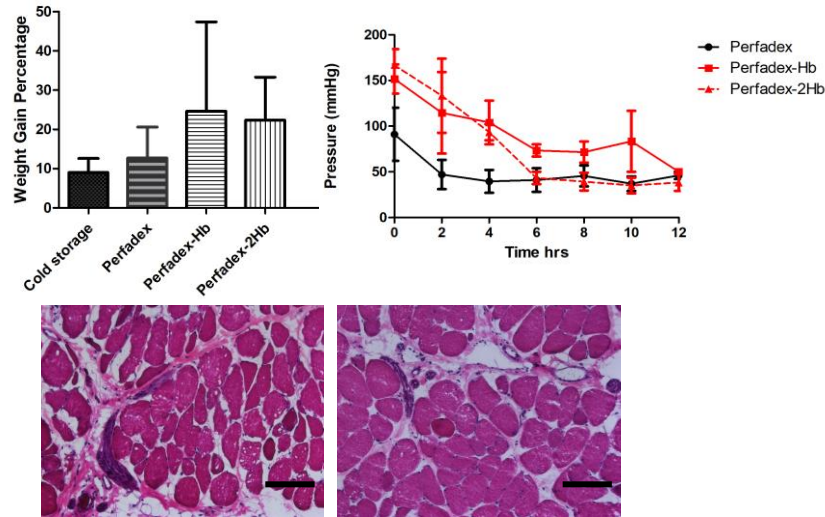


Figure 9. A. Weight gain of grafts after 12 hours of ex-vivo perfusion with Perfadex or Perfadex-acellular hemoglobin (5, 11 gr/dL) B. Perfusion Pressure C.H&E-stained muscle perfused by Perfadex-acellular hemoglobin (5gr/dL)

Extend ex-vivo perfusion to 24 hours

The 12-hour perfusion protocol with Perfadex has shown promising result in terms of perfusion-induced damage. We have extended the same protocol to conduct 24-hour sub-normothermic ex-vivo perfusion, but tissue swelling increased significantly. Two strategies were tested to lower edema: decreasing flow rate (by two third) and increasing colloid concentration (by half). Tissue swelling was still above 20% which demonstrates that swelling rate exacerbates with time and different approach should be taken. Since ischemic damage increases dramatically by time, we speculate providing oxygenation and lowering ischemic damage play critical role as perfusion times extends beyond 12 hours. Thus, we need to incorporate oxygenation before extending perfusion time.

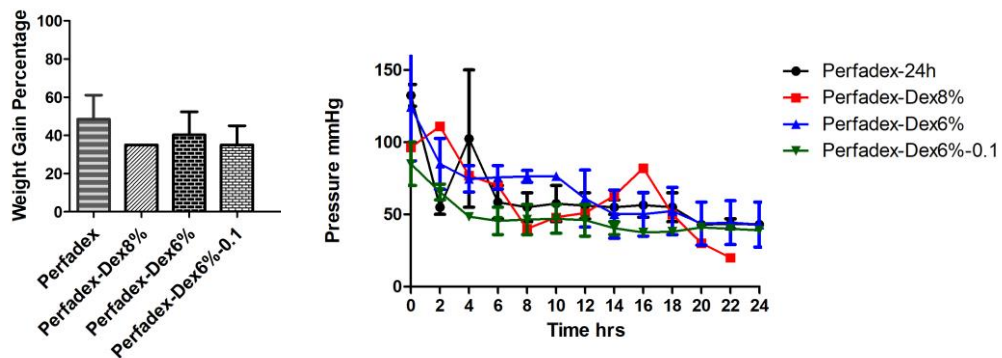


Figure 10. Increased Colloid concentration (Dextran 6%, 8% wt(n=1)) and decreased flow rate (0.1 ml/min) impact on graft swelling and perfusion pression after 24 hours of ex-vivo perfusion.

Discussion of stated goals not met

Implementing oxygenation into the ex-vivo perfusion system by adding modified hemoglobin-based oxygen carrier due to COVID-19 shutdown which paused our operation for several months

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.

Courses:

One-on-one work with mentor has 2 one-on-one meetings each year with Sara Salehi to discuss project related elements as well as all other factors related to professional development.

Weekly or bi-weekly meetings: Dr. Grayson has had weekly meeting with Sara Salehi to discuss challenges of ex-vivo perfusion system as it started getting increasingly complex

Monthly Meeting : The progress made by each Dr. Grayson, Brandacher and Slaughter labs has been discussed every month with everyone working on the project.

Papers:

Meetings with clinicians: Sara Salehi has had monthly meetings with Dr. Brandacher to discuss issues with VCA procurement, perfusion and transplantation surgery.

Conferences: Nothing to report

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.

- Develop electrical stimulation protocol to improve tissue perfusion. We will conduct a controlled study to test two electrical stimulation protocols.
- Implement oxygenation into ex-vivo perfusion. We will investigate the optimum oxygen carrier concentration with modified acellular hemoglobin from our collaborator. Oxygen transfer dynamic, metabolism rate and oxygen carrier dissociation/absorption rate will also be studied.

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 Project Director/Principal Investigator (PD/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. 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.

Nothing to report

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.

Restriction imposed by Johns Hopkins University because of COVID-19 pandemic impacted our operation. For instance restricting the number of personnel who could work in the lab slowed down experiments and evaluations.

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.

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

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

5. **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

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).*

abstract
“Establishing a Rat Abdominal Wall Perfusion Model for VCA Preservation”, Organ Banking Summit, 3rd-6th August 2017

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.*

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.

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;*
- *biospecimen 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

6. 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.”

Example:

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	Project Role	Researcher Identifier (e.g. ORCID ID):	Nearest person month worked	Contribution to project
Warren Grayson	Principal Investigator	0000-0001-6099-6469	3	Performed work towards bioreactor design. Worked on perfusion system process design.
Gerald Brandacher	Co-Investigator		1	Worked on animal model development
Byoung Chol Oh	Co-Investigator		1	
Gymama Slaughter	Co-Investigator		2	Worked on biosensor design
Sara Salehi	Graduate Student		12	Build perfusion system, establish abdominal wall perfusion and viability assessment
Joseph Lopez	Plastic surgery resident		1	Developing of perfusion system, small animal surgery, viability assessment methods and designing Bioreactor
Richa Kalsi	Post-Doctorate Fellow		1	
Yichuan Zhang	Lab Assistant		2	Assistance with viability assessment, in vitro data analysis

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.

Gerald Brandacher	Change: Ended – W81XWH-16-C-0212 - Phase II: Novel Super-cooling of Genitourinary Cells and Tissues for Transplant Role: Site PI Effort: 1.08 CM Date: 10/01/2018 – 05/24/2020
Gerald Brandacher	Change: Ended – W81XWH-16-1-0708 - Engineering a Hybrid Thymus to Unravel the Tolerogenic Properties of Vascularize Role: Co-I Effort: .12 CM Date: 09/30/2016 – 06/29/2020
Gerald Brandacher	Change: New - 2020-MSCRFL-5414 - Human iPSC-derived EGFR+ functional Schwann Cells to Enhance Nerve Regeneration Role: Co-I Effort: .12CM Dates: 06/30/2020 – 06/29/2022

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:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (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.*

Nothing to Report.

7. 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. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

Nothing to Report.

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

8. **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.

Nothing to Report.