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TITLE: The Johns Hopkins RTR Consortium: A Collaborative Approach to Advance Translational Science and Standardize Clinical Monitoring of Restorative Transplantation

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
The overall goal for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The Consortium has thus assembled three complimentary, multidisciplinary research projects from Johns Hopkins, Massachusetts General Hospital and University of Pittsburgh. Each of the individual projects has made significant progress during this reporting period. The Initiating Site through their coordinated efforts has facilitated that all projects are mostly on track with the proposed statements of work. The group has met all Major Tasks for Year 2, in particular we have assisted sites with ACURO and HRPO submissions, contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly Reports and held update calls to discuss progress among project leaders.
TABLE OF CONTENTS

1. INTRODUCTION ..................................................................................................2
2. KEYWORDS ..........................................................................................................3
3. ACCOMPLISHMENTS ........................................................................................3
   a. Major Goals
   b. Accomplishments Under these Goals
   c. Opportunities for Training and Professional Development
   d. Dissemination of Results
   e. Plans for Next Reporting Period
4. IMPACT ...............................................................................................................10
   a. Impact on the Development of the Principal Discipline(s) of the Project
   b. Impact on Technology Transfer
   c. Impact on Society Beyond Science and Technology
5. CHANGES/PROBLEMS ....................................................................................11
   a. Changes in Approach
   b. Problems/Delays and Plans for Resolution
   c. Changes that Impacted Expenditures
   d. Changes in use or care of vertebrate animals, biohazards, and/or select agents
6. PRODUCTS..........................................................................................................12
   a. Publications
   b. Websites
   c. Technology or Techniques
   d. Inventions
   e. Other Products
7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS ..........15
   a. Individuals
   b. Changes in Active Other Support of PI
   c. Partner Organizations
8. SPECIAL REPORTING REQUIREMENTS ......................................................16
   a. Collaborative Awards
   b. Quad Charts
9. APPENDICES ......................................................................................................16
INTRODUCTION

Restorative Transplantation has emerged as a new modality to restore both function and form following devastating injuries to the face and upper extremities in a way not previously possible. Despite initial success, great challenges remain in ameliorating long-term immunosuppression, understanding acute and chronic rejection, and optimizing immune monitoring and perioperative protocols. As the field of Restorative Transplantation matures, significant opportunities are emerging for transplant researchers and clinicians to capitalize on the unique features of VCA, glean from advances and experience in solid organ transplantation (SOT), and achieve genuine progress in transplant outcome and patient safety. The Johns Hopkins RTR Consortium has thus assembled some of the world’s most renowned scientists, researchers, and surgeons in vascularized composite allotransplantation (VCA) research to address some of the most relevant and pressing research areas in reconstructive transplantation.

The overall goal for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners. The central hypothesis is that the maturing field of Restorative Transplantation will benefit the most from the establishment of a multi-institutional, multi-disciplinary collaborative consortium that builds on knowledge and experience derived from the study of SOT to address the unique challenges and opportunities presented in this new field.
2. **KEYWORDS**
Vascularized Composite Allotransplantation
Immunoregulation
Tolerance
Rejection
Ischemia Reperfusion
Cell based Therapy
Large animal models
Allograft
Hand Transplantation
Face Transplantation

3. **ACCOMPLISHMENTS**

The Initiating Site has met all Major Tasks for the project as outlined in the Statement of Work. In particular, we have assisted sites with ACURO and HRPO submissions, No Cost Extensions (NCE), contacted sites to remind them of upcoming Quarterly Report deadlines, Collected and Reviewed Quarterly and Annual Reports and held update calls to discuss progress among project leaders.

The accomplishments for each of the individual projects have been summarized in detail in their separately submitted final project reports. A summary of key findings from each project is outlined below:

**Johns Hopkins University (MR120034P10)**

The group investigated a belatacept-based protocol to enable calcineurin inhibitor (CNI) minimization/avoidance (Aim 1) after heterotopic swine hind-limb allotransplantation across a full SLA mismatch and furthermore set out to examine the efficacy of transitioning to belatacept (CTLA4-Ig) maintenance therapy from a calcineurin inhibitor based immunosuppression regimen (Aim 2) and to compare immunomodulatory donor BM infusion to BM transplantation with establishment of durable mixed chimerism for induction tolerance and/or VCA survival on CNI free immunosuppression using a belatacept-based regimen (Aim 3).

Specifically, **Aim 1:** Group I was treated with high-dose tacrolimus (15-20ng/ml) maintenance therapy. Group II was treated with low-dose tacrolimus (4-6ng/ml). Group III received low-dose tacrolimus and 20 mg/kg of CTLA4-Ig administered on POD2, 7, 14, 30, 60, 90, and 120. **Aim 2:** Group IV received transient high-dose tacrolimus until POD60. Group V received transient high-dose tacrolimus until POD60 and was switched to CTLA4-Ig administered on POD60, 85, 100, 120 and 150. **Aim 3:** Group VI received the non-myeloablative conditioning plus bone marrow infusion (BMI) and intermediate dose tacrolimus (10-15 ng/ml) for 30 days only. Group VIII received the induction regimen, BMI and CTLA4-Ig and a short-term dose of tacrolimus (30 days). In all groups, graft rejection was monitored by clinical assessment and protocol skin biopsies. Alloreactivity
against donor antigens was assessed using an optimized CFSE-based mixed lymphocyte reaction (MLR).

All Group I animals died prematurely due to infectious complications related to high dose tacrolimus treatment. 2/3 animals that received sub-therapeutic tacrolimus (Group II) rejected their grafts. 3/5 animals who received belatacept in addition to low dose tacrolimus (Group III) achieved long term graft survival (>230 days). 3/3 animals in Group IV and 4/5 animals in Group V achieved indefinite graft survival (beyond POD300) despite weaning of all immunosuppression. The one animal in Group V that rejected its graft began to show evidence of rejection on POD277. During Aim 3, a total of 6 animals were transplanted in Group VI. Three animals in this group were euthanized before day 30 due to complications (bleeding, hematoma, and post-transplant lymphoproliferative disorder). Two animals in Group VI display long-term graft survival >350 days, while one animal displayed signs of mechanical trauma approximately around POD 300, triggering loss of the whole graft by POD365. Donor specific unresponsiveness was confirmed in all long-term survivors in vitro by CFSE-MLR. Two animals were transplanted in Group VIII. Both animals completed their course of CTLA4-Ig and were maintained on high-dose tacrolimus after transplant but developed lethargy, anorexia, neutropenia, and respiratory distress and were euthanized before POD20. Pathology findings have identified radiation-related cardiac injury as a potential contributor to their clinical outcomes.

Overall, these results indicate that the addition of CTLA4-Ig to subtherapeutic CNI does not appear to be able to prevent graft rejection. However, tolerance of VCA containing a vascularized bone component may be achieved with a conditioning regimen of non-myeloablative irradiation and peritransplant tacrolimus. Furthermore, the long-term graft survival off of immunosuppression for animals treated with low-dose or high-dose tacrolimus suggest that the vascularized bone component of the composite graft may have a more robust immunomodulatory effect than expected.

Achievements:

- Unexpected long-term graft survival of animals receiving a VCA combined with short-term immunosuppression, i.e. high-dose tacrolimus, yielded scientifically promising results in this project. Graft survival significantly exceeded the investigators expectations resulting in long-term/indefinite graft survival in some of the experimental groups. The detailed data outlined in the final report highlights the powerful immunomodulatory contributions of grafts containing vascularized bone marrow and indicate that these grafts may be more conducive to immunosuppression sparing protocols as well as tolerance induction.

- The addition of CTLA4-Ig to subtherapeutic CNI does not appear to be able to prevent graft rejection. Tolerance of VCA containing a vascularized bone component may be achieved with a conditioning regimen of non-myeloablative irradiation and peritransplant tacrolimus. In addition, unexpected results have shown that indefinite graft survival can be achieved subsequent to induction and transient high-dose tacrolimus monotherapy in VCAI containing a vascularized bone marrow component or with additional donor bone marrow cell infusion. This
could allow the development of alternative protocols devoid of the well-known and documented toxicities and side effects of CNIs, which are currently hampering broader application of these life changing reconstructive modalities.

- There are currently no publications showing successful staining for Foxp3 in swine skin. The investigators have been able to produce replicable Foxp3 staining in both swine lymphoid tissue as well as swine skin. This was achieved through slowing the heat-induced epitope retrieval process and tightly regulating the temperature using a water-bath instead of common heating methods as well as blocking with hydrogen peroxide after incubation with the primary antibody. The group identified significant population of Foxp3+ regulatory T cells in the skin of severely rejecting grafts, but few to no positive cells in mild-moderate rejected grafts.

Progress against SOW:

- As detailed in the Final Report

Challenges:

- Delays in animal availability from the breeder at Massachusetts General Hospital (MGH) have accumulated to contribute to delayed completion of in-vivo as well as associated in-vitro experiments during Year 3 of this project. Therefore, a NCE was been submitted and the past 12 months were utilized to finalize the histology and immunohistochemistry data to determine graft infiltrating immune cell phenotypes, immune phenotyping of PBMCs using FACS, and chimerism analysis. These additional experiments and data analysis have been performed in conjunction with their collaborators at MGH.

- The CFSE-MLR assays represented a prolonged challenge due to the inability to consistently obtain adequate stimulation of responder cells. A systematic and analytical approach was undertaken to allow optimization of the assay, which required numerous modifications to the original protocol.

- Pathology findings have identified radiation-related cardiac injury as the possible contributor to the clinical outcome of two animals in group VIII. The development and use of a radiation-free protocol is therefore warranted in the future to reduce induction regimen-related mortality.

- The investigators were not able to complete all the proposed experimental groups investigating the tolerogenic effects of combined BMI and peri-transplant CTLA4-Ig (traditional and intensified) due to initial animal deaths related to complications of the regimen that required repeat transplants.

Massachusetts General Hospital (MR120034P10 Subaward to JHU)
Previously, the laboratory at MGH has shown that durable mixed chimerism can be achieved through a protocol consisting of 100 cGy total body irradiation, T-cell depletion, and the transplantation of cytokine-mobilized peripheral blood mononuclear cells (CM-PBMCs). With this regimen, the investigators could achieve tolerance of all components of a fasciocutaneous VCA (epidermis & dermis) across single haplotype full mismatch,
and class I matched/class II mismatched MHC barriers. However, across class I mismatched/class II matched MHC barriers, rejection crises developed despite durable mixed chimerism and in vitro unresponsiveness to donor antigens. Therefore, the group’s current goal was to study also the contribution of vascularized bone marrow (as part of the hind limb) and CoB in overcoming class I mismatch/class II match MHC barriers for VCA tolerance.

Achievements:

- The group’s results suggest that the combination of vascularized bone marrow, costimulatory blockade (CoB), and donor bone marrow cells appears sufficient in preventing rejection episodes in a pre-clinical large animal model.
- However, this observation is confounded by the immunomodulatory effect of donor bone marrow, and the co-administration of tacrolimus for the first 30-45 days of the experiment.
- Further follow-up of the current surviving animal will be key in determining the efficacy of CoB-based regimens.

Progress against SOW:

- As detailed in the Final Report

Challenges:

- One swine had an anesthetic death (POD 9) at the time of a biopsy procedure. Another swine was euthanized due to a line infection that was refractory to wide specter antibiotic therapy, which is a risk with indwelling central lines. Another animal succumbed to respiratory distress on POD 33 and necropsy findings were that of an abscess at the line insertion site at the internal jugular vein.
- Two animals experienced lung complications that presented as idiopathic pulmonary syndrome (IPS). This may have been due to the release of cytokines IL-6 and IL-17. The investigators have proposed to incorporate IL-6 receptor blockade (tociluzimab) into their regimen.

The investigators conclude in their Final Report that use of CoB may potentially allow single-CNI maintenance regimens following VCA, compared to current regimens based on triple immunosuppression with CNI, steroids and mycophenolate mofetil. The addition of borderline myeloablative thymic and total body irradiation serves to deplete allo-reactive cells within the recipient’s thymus and bone marrow in order to promote the likelihood of engraftment following BMT to generate a state of mixed chimerism. This contrasts with current clinical strategies whereby induction therapy typically incorporates depletion of circulating T cells with either monoclonal or polyclonal antibodies (e.g. ATG, alemtuzumab). Clinical application is still unlikely due to legitimate concerns of pancytopenia and the resulting hematological and infective sequelae with such high dose irradiation. However, should the results from this project be successful once final analysis
is completed, it may provide proof-of-concept of CoB-based tolerance induction strategies that may reduce the overall burden of immunosuppression required in VCA.

**Massachusetts General Hospital (MR120034P5)**

The investigators aimed in this project to introduce and optimize a protocol for VCA tolerance based on the principle of delayed induction of mixed chimerism in a non-human primate (NHP) model. This approach, in contrast to protocols which are currently evaluated in clinical trials for kidney transplantation, permits induction of tolerance in the context of transplantation from deceased donors which represents a prerequisite for clinical application in VCA.

Two delayed tolerance regimens were investigated an initial protocol with a cohort of four recipient animals on 4-month maintenance immunosuppression and a second cohort of six recipient animals with 2-month maintenance immunosuppression. The results with regard to allograft survival, incidence of acute and chronic rejection, levels of chimerism, alloreactivity as assessed by mixed lymphocyte reaction, and incidence of donor reactive antibodies as well as characterization of skin resident leukocytes are detailed in the investigator’s Final Report.

**Achievements:**

- The investigators have established a NHP orthotopic upper extremity transplant model that has been utilized for the initial phase of the project. However, in light of technical difficulties and the number of technical failures (n=4) that were encountered the team decided to switch to a heterotopic partial face transplant model for the remainder of the study.
- The group has shown successful short-to-medium term withdrawal of immunosuppression in a clinically relevant NHP model of VCA. However, more successful engraftment strategies will be required as transplant tolerance could not be induced.
- By reducing the delayed tolerance protocol from the original 4 months to 2 months, the investigators have reduced the number of acute rejection episodes and were able to avoid rejection completely in haploidentical recipient animals.
- Decreasing the delay period has also allowed to reduce the overall duration of exposure to high-dose immunosuppression and thus the risks of related complications such as PTLD and cachexia.
- The investigators have optimized techniques for analysis of the cutaneous immune system in non-human primates. These techniques permit comparative analysis of skin immune responses in multiple research species and in humans, which will facilitate broad translation of findings from this work.

**Progress against SOW:**

- As detailed in the Final Report
Challenges:

- The investigators have encountered a concerningly high incidence of post transplant lymphoproliferative disease (PTLD) of 50% (5/10 recipient animals) in this study. This has been in previous studies also attributed attributed to the high incidence of PTLD in NHP studies of VCA to simian lymphocryptovirus (LCV). This will need to be taken into consideration for future experiments that might require the use of extensive ganciclovir prophylaxis, use of rituximab for B cell depletion, or to replace ATGAM (largely T cell depletion) with alemtuzumab (depletes both T and B cells).

- The investigators encountered in several cases development of chronic rejection in their NHP model. This finding is in line with recent similar reports emerging from long-term follow-up of VCA patients with face and upper extremity transplants.

Conclusion:

The induction of transplant tolerance for reconstructive transplantation would be of considerable benefit to civilian victims of disabling and disfiguring tissue loss, and of significant importance to military victims of upper extremity and/or craniofacial trauma. Currently, the necessity of life-long immunosuppression and regular medical monitoring would prevent recipients of restorative transplants (such as hand or face transplant) from returning to active duty, but a safe and effective protocol for induction of transplant tolerance holds the potential to fundamentally change this paradigm.

The development of acute rejection during the delayed period in the protocols evaluated in this project is likely the main factor preventing donor bone marrow cell engraftment. Based on the literature, sensitization of the recipient against donor cells reduce the chance of these cells to engraft. Future strategies will evaluating to change to day 0 BMT and adjust the treatment to avoid PTLD.

University of Pittsburgh (MR120034P4)

The investigators have accomplished all specific aims as detailed in their Final Report. The group was able to demonstrate the significant advantages of their machine perfusion (MP)/oxygen carrier (OC) system when compared to cold storage over an extended preservation time period (CIT=14 hours). Effective ex-vivo oxygenation with the investigator’s MP/HBOC system allows VRAM transplantation after 14 hours of preservation without significant damage to the graft.

Achievements:
This project has allowed the investigators to significantly extend preservation times (14 hours) for VCA, while showing the clear superiority of this preservation modality when compared to the current standard of care (CSP). These findings should have major implications in upcoming clinical applications of this technology.

The group developed and patented and new MP device for CVA based on these initial proof-of-concept experiments. This IP has already been licensed by VirTech Bio (VTB) Inc., Natick, MA.

The group developed a new human-based OC solution through a SBRI/NIH Phase 1 award. This new solution has been recently validated in our lab through a corporate research agreement with VTB.

Progress against SOW:

- As detailed in the Final Report

Conclusions:

The MP/HBOC system can effectively preserve VRAM allografts when compared to CSP. MP/HBOC significantly mitigates IRI, which was detected earlier within the first 4 hours in the CSP group. Effective ex-vivo oxygenation with HBOC decreases post-transplant inflammation in skeletal muscle fibers and upregulates regenerative metabolic pathways driving early recovery from IRI. There is a similar up-regulation of TNF-α in the CSP group, which is similar to the group’s previous data obtained in liver allografts after a period of 9 hours of preservation. Effective ex-vivo oxygenation with the MP/HBOC system avoids the early (hours) formation of hypercontracted sarcomeres (CB) and the subsequent development (days) of myofiber necrosis, myopathic changes, edema and hemorrhage seen extensively in CSP as the current standard of care. The significant IRI observed in the CSP group yielded a significant hypereosinophilic sarcomere degeneration leading into irreversible loss of muscle fibers, followed by progressive granulomatous inflammation accompanied by the infiltration of large, activated macrophages, epithelioid macrophages and multinucleated giant cells, leading into terminal mineralization and complete loss of muscle mass.

Metabolic precursors of nucleotide synthesis were significantly upregulated in the MP/HBOC group. These precursors appear to be implicated in a strong regenerative response elicited by effective oxygenation of skeletal muscle, which also has a positive impact in energy utilization and ROS scavengers. The MP/HBOC also promoted effective ex vivo oxygenation and shifted skeletal muscle metabolic profile from β-oxidation towards Ω-oxidation during VCA preservation when compared to the prolonged anoxia under hypothermic conditions induced by CSP. This can be interpreted as a sign of mitochondrial dysfunction experienced by the CSP group. In fact, Ω-oxidation is linked to balanced redox state and less oxidative
damage during stressful conditions induced by these experiments. In contrast, CSP appears to increase a reactive skeletal muscle β-oxidation pathway, which leads into oxidative damage and disintegration of cellular membranes when prolonged hypothermia, anoxia, and limited glucose supply is imposed. Contrary to the CSP group, MP/HBOC protects skeletal muscle against early graft myopathy. These complex metabolic features seen in the both the muscle and adipose tissue were extensively corroborated by the serial histological findings, revealing in a close analogy the same protective role exerted by effective ex-vivo oxygenation documented extensively in our previous liver experiments.

a. What were the major goals of the project?

The overall goal for the Johns Hopkins RTR Consortium is to advance translational research of the most clinically pertinent issues of Restorative Transplantation through a multidisciplinary collaboration among highly experienced and accomplished partners.

b. What was accomplished under these goals?

Each of the individual projects has made significant progress as detailed above and in the individual Final Reports. The Initiating Site through their coordinated efforts has facilitated that all projects were mostly on track with the proposed statements of work. No Cost Extensions (NCEs) were requested and granted for two of the three projects. The Initiating Site has coordinated efforts and increased the frequency of project leader conference calls to ensure timely completion of the tasks as outlined in the statement of work during the NCE.

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

Please refer to individual Final Project Reports.

d. How were the results disseminated to communities of interest?

The data and findings from the individual projects were shared in form of multiple oral and poster presentations at national and international scientific meetings as well as were disseminated through published manuscripts in peer reviewed scientific journals.

e. What do you plan to do during the next reporting period to accomplish the goals?

Not applicable

4. IMPACT:

a. What was the impact on the development of the principal discipline(s) of the project?
Please refer to individual Final Project Reports

b. What was the impact on other disciplines?

Please refer to individual Final Project Reports

c. What was the impact on technology transfer?

Please refer to individual Final Project Reports

d. What was the impact on society beyond science and technology?

Nothing to report

CHANGES/PROBLEMS:

a. Changes in approach and reasons for change

Nothing to report.

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

Nothing to report.

c. Changes that had a significant impact on expenditures

Nothing to report.

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

Nothing to report.

d. Significant changes in use or care of human subjects

Nothing to report.

e. Significant changes in use or care of vertebrate animals.

Nothing to report.

f. Significant changes in use of biohazards and/or select agents

Nothing to report.
5. PRODUCTS

Publications and Abstracts:


Fontes P, Gorantla V, Plock J, Davis M. Ex-vivo perfusion of vascularized composite allografts at 21°C with a hemoglobin-based oxygen carrier (HBOC) solution over 14 hours: new opportunities for effective en-route care. NATO Symposium on "Regenerative Medicine and advanced Rehabilitation - Today and in Future" (HFM-272) October, 2016, Brussels, Belgium.

Ng ZY, Read C, Kurtz JM, Cetrulo CL Jr. Memory T cells in vascularized composite allotransplantation. Vasc Compos Allotransplantation 2015;2(4):75-79.

Lellouch AG, Ng ZY, Gama AR, Schol IM, Randolph MA, Kurtz JM, Cetrulo CL Jr. CTLA4-Ig, Vascularized bone marrow and donor bone marrow cells successfully negate the development of acute skin rejection of vascularized composite allografts in MHC class-I-mismatched Recipients New England Society of Plastic and Reconstructive Surgeons 2017

Ng ZY, Lellouch AG, Schol IM, Gama AR, Leonard DA, Powell H, Defazio MW, BS; Randolph MA, Tan BK, Sachs DH; Kurtz JM, Cetrulo, Jr. CL, Towards Tolerance of Vascularized Composite Allografts – Development of Clinical Mixed Chimerism-Based Protocols in Swine Surgical and anesthesia Congress (Singapore) 2017 Singhealth (Awarded Best Abstract)

Schol IM, Lellouch AG, Ng ZY, Gama A, Randolph M, Kurtz JM, Cetrulo CL Jr. CTLA4-Ig, vascularized bone marrow and donor bone marrow cells successfully negate the development of acute skin rejection of vascularized composite allografts in MHC class I mismatched recipients. American Transplant Congress, Chicago, IL; 30 April 2017

Schol IM, Ng ZY, Lellouch AG, Gama A, Randolph M, Kurtz JM, Cetrulo CL Jr. CTLA4-Ig, vascularized bone marrow and donor bone marrow cells successfully negate the development of acute skin rejection of vascularized composite allografts in MHC class I mismatched recipients. American Surgical Association, April 2017

Schol IM, Lellouch AG, Ng ZY, Gama A, Randolph M, Kurtz JM, Cetrulo CL Jr. CTLA4-Ig, vascularized bone marrow and donor bone marrow cells successfully negate the development of acute skin rejection of vascularized composite allografts in MHC class I mismatched recipients. MHSRS 2017


Lellouch AG, Ng ZY, Schol IM, Rosales IA, Leonard DA, Powell H, Gama AR, Colvin RB, Kurtz JM, Cetrulo, Jr CL Delayed Induction of Tolerance to Vascularized Composite Allografts in Non-Human Primates: Immunomodulation with Bone Marrow Transplantation and Tocilizumab


Ng ZY, Defazio MW, Powell H, Leonard DA, Heroux ZW, Lellouch AG, Cetrulo CL Jr, Kurtz JM. Analysis of acute skin rejection in non-human primate models of face and hand allotransplantation. Oral Presentation. 26th International Congress of The Transplantation Society, Hong Kong; 23 August 2016

Ng ZY, Lellouch AG, Defazio MW, Heroux ZW, Shah JA, Kurtz JM, Cetrulo CL Jr. Immunomodulation in vascularized composite allotransplantation – preliminary results in a non-human primate model with tocilizumab. American Society of Plastic Surgeons Annual meeting, Los Angeles, CA; 24 September 2016 (Awarded Outstanding Paper Presentation in Research & Technology Track)

Rosales IA, Defazio M, Foreman RK, Sachs DH, Cetrulo CL, Colvin RB, Leonard DA Systematic pathological component scores for skin-containing vascularized composite allografts 13th Congress of the International Society of Vascularized Composite Allotransplantation 2017

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name: W. P. Andrew Lee
Project Role: Principal Investigator
Nearest Person Month Worked: 5% (0.6 calendar months)
Contribution to Project:

Name: Gerald Brandacher
Project Role: Co-Investigator
Nearest Person Month Worked: 5% (0.6 calendar months)
Contribution to Project:

Name: Rochelle Smith
Project Role: Assistant Grant Administrator
Nearest Person Month Worked: 40% (4.8 months)
Contribution to Project: Rochelle Smith drafts reminder emails to send to each site prior to report submission deadlines, coordinates with the PIs to obtain updated information, maintains financial records, and oversees project progress with the Scientific Director and PI.

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

Nothing to Report

c. Partnering Organization

Johns Hopkins University (MR120034P10)
Gerald Brandacher, MD
d. SPECIAL REPORTING REQUIREMENTS

   a. **QUAD CHARTS**: Attached.

   e. **APPENDICES**

      Nothing to Report.