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TITLE: Adult Tissue-Derived Stem Cells and Tolerance Induction in Nonhuman Primates for Vascularized Composite Allograft Transplantation

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RECIPIENT: Uniformed Services University of the Health Sciences (USUHS)
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14. ABSTRACT

Amputations and unsalvageable injuries with devastating tissue loss are common in the combat wounded. Reconstructive transplantation in the civilian setting using vascular composite allotransplants (VCA) composed of multiple tissues (skin, muscle, nerve, bone) in combination with long-term multidrug immunosuppression has been encouraging. However, the success of hand and face vascularized composite allografts (VCA) depends on high levels of immunosuppressive medications. The ability to minimize the high risks of both rejection episodes and immunosuppressive medications could allow for safer and more widespread VCA application to wounded service members.

15. SUBJECT TERMS
vascularized composite allografts (VCA), vascularized bone marrow (VBM), non-human primate (NHP), adipose-derived stromal cells (ASC), Face transplant, Hand transplant, Rejection, Immunosuppression, Tolerance, Chimerism

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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W81XWH-16-2-0042: Adult Tissue-Derived Stem Cells and Tolerance Induction in Nonhuman Primates for Vascularized Composite Allograft Transplantation-the VCA

I. INTRODUCTION

Amputations and unsalvageable injuries with devastating tissue loss are common in the combat wounded. Reconstructive transplantation in the civilian setting using vascular composite allotransplants (VCA) composed of multiple tissues (skin, muscle, nerve, bone) in combination with long-term multidrug immunosuppression has been encouraging. However, the success of hand and face vascularized composite allografts (VCA) depends on high levels of immunosuppressive medications. The ability to minimize the high risks of both rejection episodes and immunosuppressive medications could allow for safer and more widespread VCA application to wounded service members.

We had previously demonstrated in a murine skin allograft transplantation model that human adipose-derived stromal cells (ASC) when used in concert with immunological conditioning support engraftment of limited numbers of donor bone marrow cells (dBMCs) across major histocompatibility complex (MHC) barriers, and lead to stable multilineage mixed-chimerism and skin allograft tolerance without the need for long-term immunosuppression. We applied these findings to an established non-human primate (NHP) platform of facial VCA that supports a role for the co-transplanted vascularized bone marrow (VBM) in protecting VCA grafts. The overall goal of these studies was to define whether ASCs+dBMC therapy may be a pro-tolerogenic cellular therapeutic displaying clinical efficacy for vascular composite allograft (VCA), solid organ, and hematopoietic stem cell transplant applications. This combination would allow for long term graft survival with reduced or elimination of chronic immunosuppression and the resulting multitude of adverse effects associated with such agents.

II. KEYWORDS

vascularized composite allografts (VCA)	vascularized bone marrow (VBM)	non-human primate (NHP)	adipose-derived stromal cells (ASC)	donor bone marrow cells (dBMCs)
Face transplant	Hand transplant	Rejection	Immunosuppression	Tolerance
Chimerism				

III. ACCOMPLISHMENTS

A. Major Goals

Task	Start Date	End Date	% Complete	Comments
UMB IACUC approval	10/1/16	10/19/16	100%	

DOD ACURO approval	10/16	2/22/17	100%	
Aim 1. Tissue-derived stem/progenitor cells (TSPCs) augment chimerism and promote long-term VCA graft survival			100%	4/4 surgical and experimental follow-up performed.
Aim 2. TSPC therapy allows for immunosuppression minimization and development of immunologic tolerance to VCA			100%	4/4 surgical and experimental periods completed.
Subtask 1: Additional surgical procedure of facial VCA transplant			100%	1/1 surgical procedure and follow-up

B. Revised Goals

An additional pair for facial VCA was added and revised plan was approved by ACURO/IACUC.

C. Accomplishment of Goals

During the first-year reporting period, all regulatory work was completed and approved for the preclinical non-human primate studies. This included University of Maryland, Baltimore Institutional Animal Care and Use Committee (IACUC) approval of the experimental protocol. This protocol was subsequently submitted and approved by the DOD Animal Care and Use Review Office (ACURO). After regulatory approval, competitive bids reviewed, and non-human primates were ordered and received. The quarantine period was initiated and completed (May 2017), during which animals were screened for selective immunologic mismatch by serologic and DNA methods to group recipient and donor pairs that would be used for the transplant experiments.

We initially addended the proposal to study the depletional therapeutic regimen. Two cynomolgus macaques received therapy with anti-CD4 and anti-CD8 monoclonal antibodies and busulfan in accordance with the study protocol to determine the tolerability of the treatment regimen and the degree of lymphocyte depletion. The first animal demonstrated good tolerability of the treatment regimen. CD4 populations were nearly completely depleted in peripheral blood as analyzed by flow cytometry (Fig. 1). CD8 populations were only depleted by 70%. A second animal was treated with an increased intensity of anti-CD8 antibody and demonstrated depletion of 65%. The remaining non-depleted CD8 population has been hypothesized to be part of a

memory T cell compartment that may have resistance to depletion with the utilized CD8 monoclonal antibody.

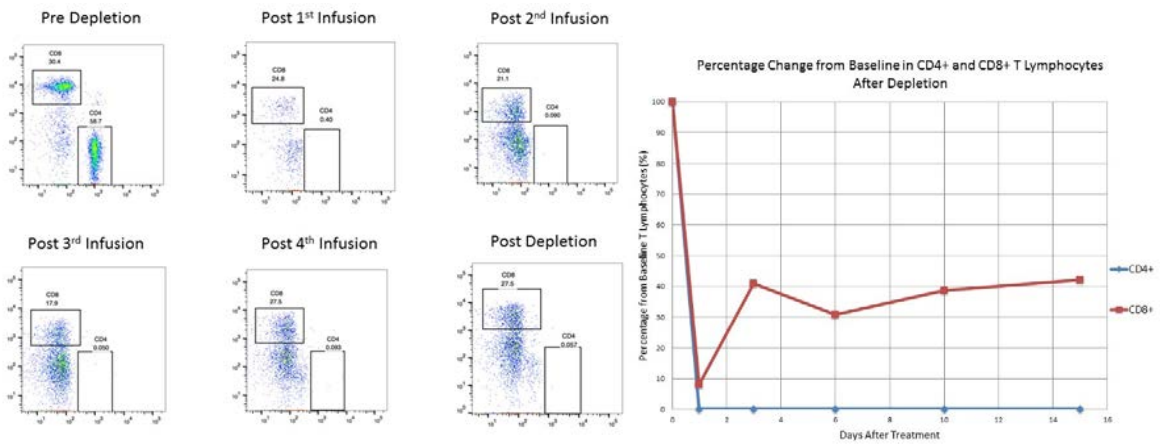


Figure 1. Depletional therapy of NHP. Anti-CD4 and anti-CD8 monoclonal antibodies were used at proposed doses to confirm biologic effect and tolerability. CD4 cells were completely depleted in the periphery with some resistance of CD8 cells based on flow cytometric analysis (left) and depletion was maintained beyond 2 weeks (right).

The experimental model was the same as previously published work consisting of heterotopic facial VCA between mismatched cynomolgus macaques (Fig 2.). The VCA was composed of skin, muscle, and bone elements. Microvascular anastomoses were performed to recipient femoral artery and vein.

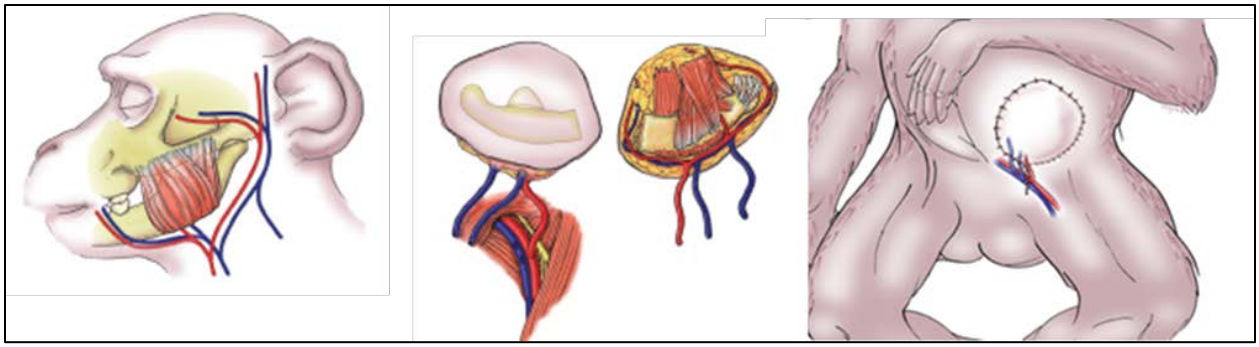


Figure 2. Non-Human Primate VCA model. Heterotopic transplant of oromandibular VCA segment with vascular anastomoses of internal and external jugular vein and common carotid artery (middle) to lower abdominal wall (right).

The protocol utilized for the experimental protocol of VCA transplant experiments utilized depletion with anti-CD4, anti-CD8, and busulfan followed by ASC and dBMC transfusion on day 7 (Fig. 3). A total of 5 animals received the initial therapies and VCA transplant. Two animals were

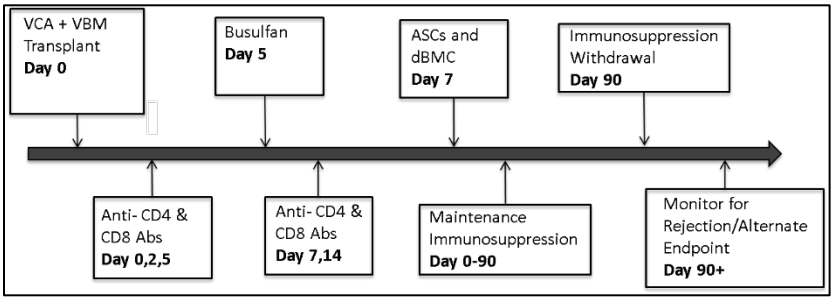


Figure 3. Experimental Protocol. Timing of lymphocyte depletion therapy and subsequent ASC and dBMC infusion. VCA transplant was performed at Day 0.

early technical failures. The animals that were able to successfully proceed through the post-operative period (n=3) demonstrated similar patterns to the prior titration and tolerability work. Early time points (day 0-7) demonstrated decreases to an average of 28.1 ± 17.6 % of baseline of CD 3+ cells, 2.9 ± 3.8 % of baseline of CD4+ cells, and 37.0 ± 31.1 % of baseline of CD8+ cells. (Fig 4). CD4 cell counts demonstrated recovery after day 21. Late (>90 days) decreases in CD4 and CD8 cell counts represented data from only one animal.

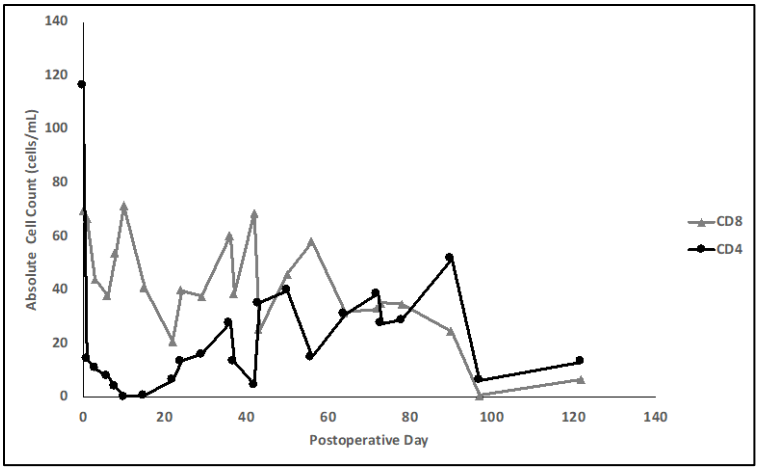


Figure 4. Cellular Depletion and Reconstitution. CD4 cells had near complete depletion early and reconstitution after 3 weeks.

Animal	Group	Survival (POD)	Banff 1+ Rejection (POD)	Maximum Chimerism (%)
1	ASC + dBMC	37	31	6.01
2	ASC + dBMC	90	59	13.48
3	ASC + dBMC	122	102	26.2

Table 1. Experimental Outcomes. Variability in rejection time points, survival, and maximum chimerism were observed in all 3 experiments. The experiment with highest chimerism levels demonstrated the best outcomes in rejection and survival.

Third party ASC's and donor-specific BMC were infused POD 7 in all three animals, with follow-up chimerism noted to be 0.84 – 26.2%. Low level chimerism persisted two weeks after completion of the cell depleting regimen, ASCs, and dBMC, with 1.37 – 7.81% of T cells donor-specific on POD 29. Maximum chimerism was 6.01 %, 13.48 %, and 26.2 % in animal 1, 2, and 3 respectively (Table 1 & Fig. 5). The experiment (Animal 3) that demonstrated the highest maximum level of donor chimerism was associated with the best outcomes of rejection-free graft survival (102 days) and animal survival until end point at day 122 secondary to post-transplant lymphoproliferative disorder.

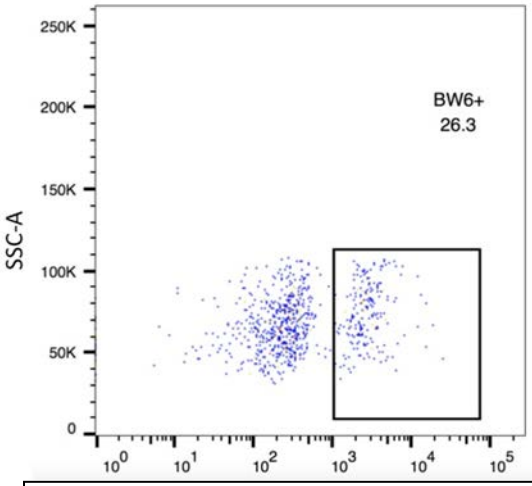
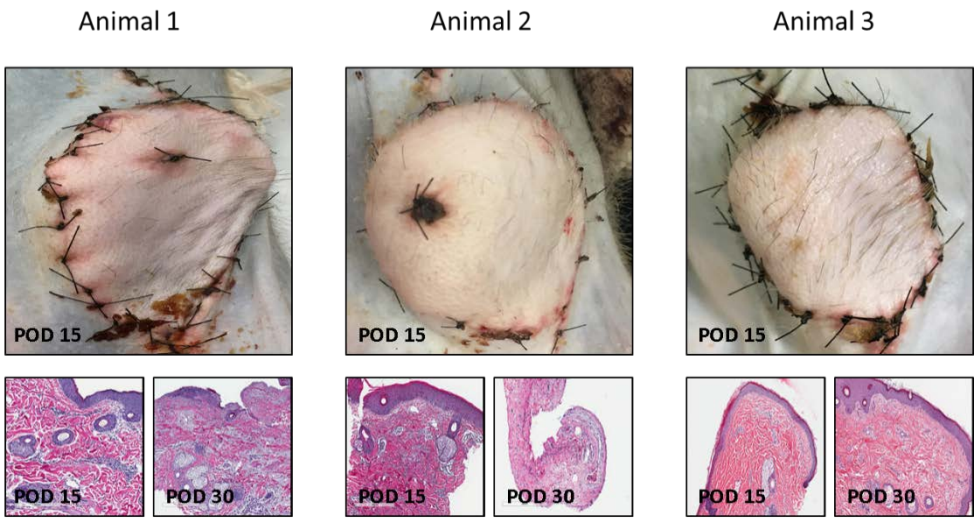


Figure 5. Chimerism. Animal 3 demonstrated the highest level of observed donor cell chimerism (Bw6 positive cells) in the periphery of 26.3% on day 22 after ASC and dBMC infusion.



VCA grafts looked healthy throughout the first weeks and up to first rejection episodes. Hair growth, lack of induration or erythema, and normal histology of biopsied skin and subcutaneous tissues were characteristic of all experiments (Fig. 6).

Figure 6. Clinical and Histologic VCA Appearance. Gross clinical appearance and biopsies at days 15 and 30 demonstrated normal, healthy VCA grafts in 3 experiments.

Immunosuppression levels were monitored and were within therapeutic ranges for all animals (15-25 ng/mL) with one animal reaching point of titration and withdrawal at day 90 (Fig. 6). Post-operatively, regulatory cell populations did not show any significant increases or association with donor chimerism levels detected in the peripheral blood (Fig. 8).

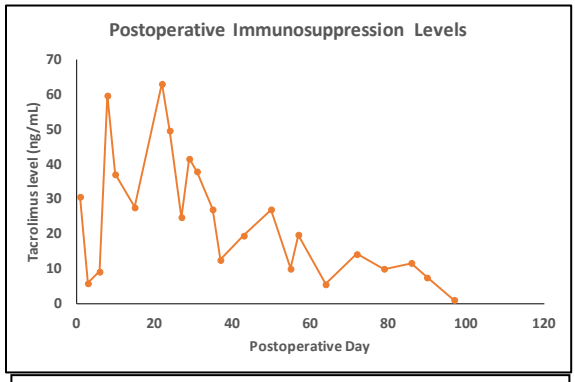


Figure 7. Tacrolimus levels. Therapeutic immunosuppression levels were achieved with elimination after day 90.

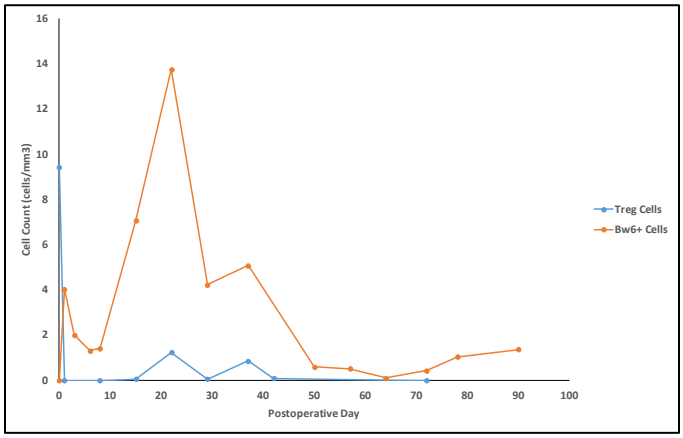


Figure 8. Chimerism and Treg populations. No increases in Treg were observed with treatment regimen.

Pro-inflammatory cytokines including interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFa) demonstrated decreases after conditioning and infusions of the ASC + dBMC product. Conversely, the same time points demonstrated increased serum levels of growth factors associated with engraftment and repopulation (Fig. 9, next page).

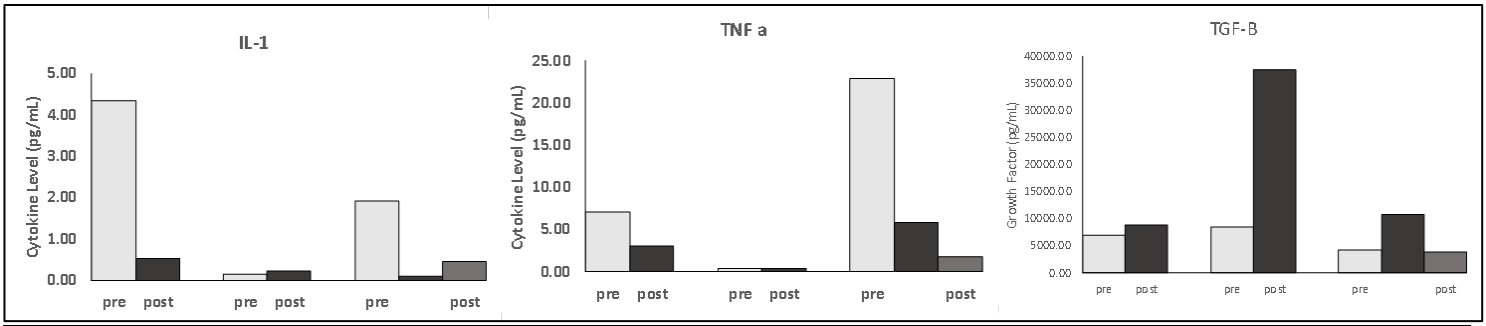


Figure 9. Cytokine profiles. Inflammatory cytokines (IL-1), TNFa) decreased post ASC therapy, with increase in growth factors (TGF-B).

Mixed lymphocyte reaction (MLR) demonstrated hyporesponsiveness of two animals that remained on immunosuppression with anti-donor responses recovering in the one animal that was withdrawn off immunosuppression at day 90 (Fig. 10). No evidence of tolerized immunologic responses could be detected based on these data and no subsequent skin grafts were able to be performed.

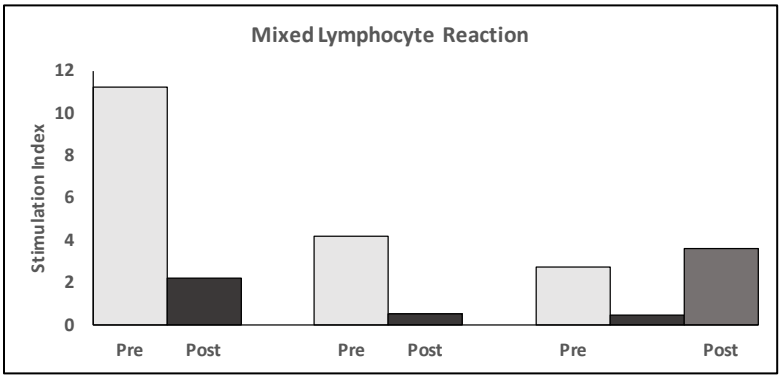


Figure 10. MLR Responses. MLR hyporesponsiveness during tacrolimus therapy (post panels) was recovered after withdrawal in one animal (right panel).

Kaplan-Meier survival plots demonstrated improved survival of ASC therapy comparable to bone marrow cell infusion alone that was performed without conditioning (Fig. 11).

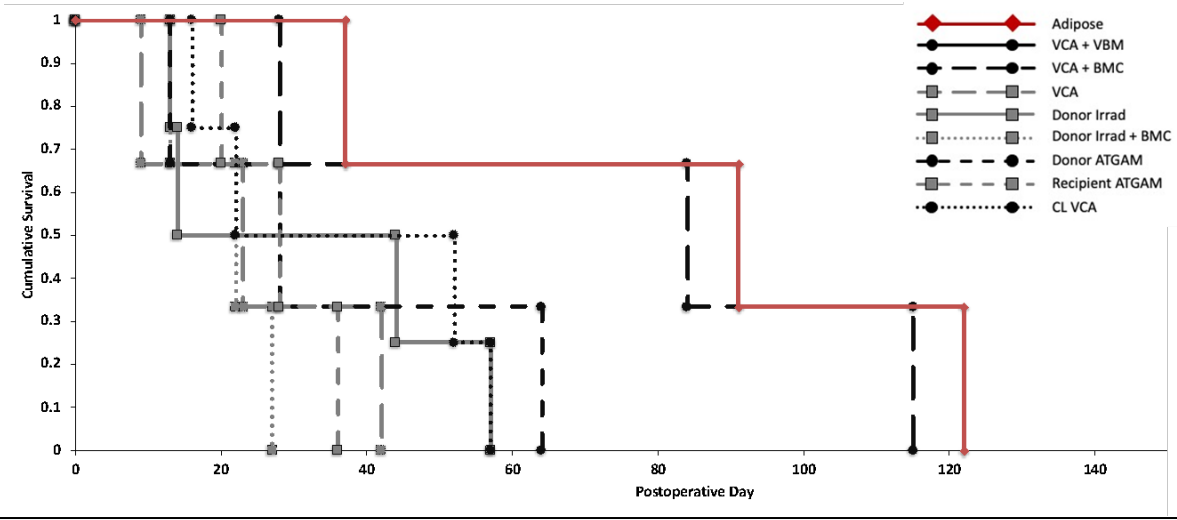


Figure 11. Kaplan-Meier Survival Plots. Adipose group (red) demonstrated prolonged survival compared to other donor or recipient interventions and comparable to BMC infusion without conditioning.

Conclusions from this study demonstrated that conditioning with ASC therapy, increased degree and duration of chimerism. The levels of donor chimerism were the highest that have been observed in the historic experience of this model of VCA. This was also associated with trends to prolonged graft survival. One animal developed post-transplant lymphoproliferative disorder that has also been historically observed in this model and associated with lymphocryptovirus infection. There is not a clear association with either the conditioning or ASC + dBMC therapy. Mechanistic studies support that adipose stem cells in conjunction with donor derived bone marrow may promote graft survival in a paracrine manner. Furthermore, ASC therapy may provide a manufactured biologic resource that can be upscaled for cellular therapeutics in transplantation and may have benefits in models of tolerance for solid organ transplants.

C1. Training and Professional Development

The laboratory has been very active in the training of research fellows and young faculty. During the period of support, two research fellows participated in funded studies. Both fellows have returned to complete surgical residencies with plans for vascular and transplant clinical fellowships. The research fellows and students have been very successful in authoring papers, chapters, and presenting at national meetings.

Our laboratory's record of accomplishment overall has resulted in training 13 graduate and post-doctoral fellows and 8 undergraduates in transplant immunology and reconstructive transplantation. They have been trained in surgical techniques of transplantation in animal models, large animal handling, immunological lab techniques, assistance with care and evaluation of clinical VCA patients, as well as the logistics of running a large animal lab. Four of these fellows have completed plastic surgery fellowships and three have academic appointments as faculty in plastic and reconstructive surgery. Two prior fellows are completing clinical fellowships in cardiothoracic surgery and plastic surgery. Finally, one of our prior post-doctoral fellows, Dr. Arthur Nam, has joined the faculty of the University of Maryland School of Medicine as a plastic reconstructive/surgeon and is a co-investigator on the current studies.

C2. Result Dissemination

Results from the laboratory's efforts in vascularized composite allotransplantation have been disseminated to national and international audiences through conferences, invited presentations, and publications as identified in Section VI.

D. Future Plans

We have completed the laboratory studies funded by 2015 Reconstructive Transplant Research (RTR) Idea Discovery Award. We are summarizing results and merging data with other studies for a manuscript describing the potential to utilize adipose-derived stem cells to improve outcomes in VCA and/or other solid organ transplants.

We have submitted an additional proposal to the RTR that were favorably reviewed but not funded. We plan to resubmit proposals to continue this work in both VCA and solid organ transplantation to both the DOD and National Institutes of Health, and to continue the robust collaboration developed during the RTR funding mechanism. Internal funding (UMB) is being used to support laboratory activities related to VCA in the interval. Additional clinical VCA efforts are underway at University of Maryland Medical Center.

IV. IMPACT

A. Impact on the Development of the Principal Discipline(s) of the Project

Impact of the studies on the field of vascularized composite allotransplantation has been through data disseminated via publications and presentations. The most important preliminary conclusion is that the combination of conditioning therapies with adipose stem cell and bone marrow transplantation results in robust donor peripheral blood chimerism, but without immunological tolerance. This approach could be significant to the field of VCA when attempting strategies to improve immunologic outcomes. Likewise, if validated, these findings may direct the planning of clinical VCA towards the inclusion of ASC + dBMC.

The main emphasis of these studies investigated clinical and experimental approaches utilizing exogenously administered cellular preparations of bone marrow and adipose stem cells. These data confirm some previous findings made in rodent models of ASC. Future study directions include enhancing the levels and duration of chimerism (either transient or stable). These findings may also lead to development of tolerance protocols This outcome would have substantial benefit to young healthy service members and civilians whom would benefit from VCA with reduced risks of chronic immunosuppression.

The unique model and immunosuppressive protocols developed by our laboratory have also informed and directed additional studies in VCA community. The specific model developed by our team of heterotopic oromandibular VCA in cynomolgus macaques has been adopted by the research team at Massachusetts General Hospital/Harvard Medical School for their studies in the field. Our immunosuppressive platform of calcineurin inhibitor based-therapy (tacrolimus) to achieve prolonged graft survival and prevent early rejection has been combined with investigations of other immunosuppressive medications that independently cannot prevent graft loss (Duke University). The concepts of vascularized bone marrow's unique immunomodulatory properties have also initiated mechanistic studies in rodents that have demonstrated many similar findings to ongoing related studies in our laboratory (University of Pennsylvania). The funded studies have succeeded in adding knowledge in one of the optimal preclinical models and

directing external research studies in the developing field of vascularized composite allotransplantation.

B. Impact on Other Disciplines

The data generated from these studies define a therapeutic approach that could allow ASC therapy to benefit other solid organ transplants. The tested hypothesis that VCA with addition of ASC therapies could develop tolerance with our immunosuppressive protocol was not supported. The tested approach did provide enhanced chimerism compared to all previously tested approaches in this VCA model. However, this was not sustained and did not prevent rejection once immunosuppression was weaned off. These results support a mechanism of ASC enhanced chimerism of donor bone marrow cells.

The techniques of NHP conditioning with anti CD4, anti-CD8, and busulfan therapy provide a tolerable and stable platform for studies in VCA and other organs. This is the first use of this combination in a NHP model of which we are aware. These techniques would benefit organ transplant and bone marrow studies in NHP. They would also have the potential for studies on immunologic tolerance that will be performed in the future in both NHP and other large animal models.

C. Impact on Technology Transfer

Nothing to Report.

D. Impact on Society beyond Science and Technology

Nothing to Report.

V. CHANGES/PROBLEMS

A. Changes in Approach and Reasons for Change

Addition of one additional experimental group secondary to peri-operative experimental termination.

B. Actual or Anticipated Problems or Delays and Actions or Plans to Resolve Them

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

Two additional experiments demonstrated early post-operative death from shock secondary to small recipient size as reviewed by thorough analysis and root cause assessment.

VI. PRODUCTS

A. Publications, Conference Papers, and Presentations

Type	Description
Conference Paper	E. Buckingham, N. Shockcor, W. Hassanein, C. Drachenberg, A. Nam, S. Bartlett, R. Barth. Mechanisms of Vascularized Bone Marrow Graft Protection of Vascularized Composite Allografts. Oral Presentation at American Transplant Congress, June 4, 2018; Seattle, WA.
Conference Paper	Shockcor, N., Buckingham, E. B., Hassanein, W., Bartlett, S. T., & Barth, R. N. (2018). Removing and Reconstituting Bone Marrow Elements Disrupts Vascularized Composite Allograft Survival. Journal of the American College of Surgeons, 227(4), S254-S255. Presented at the American College of Surgeons 2018 Annual Clinical Congress, October 22, 2018; Boston, MA.
Conference Paper	Shockcor N, Buckingham B, Hassanein W, Akinsiku B, Elster E, Davis T, Gimble J, Nam A, Bartlett S, Barth R. Adipose Stem Cells Promote Chimerism and Composite Tissue Engraftment. InAMERICAN JOURNAL OF TRANSPLANTATION 2019 Jan 1 (Vol. 19, pp. 93-93).
Presentations	Barth RN. Translational Science in VCA: Where are we Now? Sunrise Didactic: VCA: Where are we now? American Transplant Congress, June 3, 2018; Seattle, WA.
Presentations	Barth RN. VCA Translational Science Progress Report. International Society of Vascularized Composite Allotransplantation; October 26, 2017: Salzburg, Austria.
Presentations	Shockcor N, Buckingham B, Hassanein W, Drachenberg C, Nam AJ, Bartlett ST, Gir Davis T, Elster EA, and RN Barth. Adipose Stem Cells Promote Engraftment of Com Tissue Allograft. University of Maryland Department of Surgery Buxton Research Symposium. June 21, 2018.

A copy of the publication should be as an appendix of the report.

B. Website(s) or Other Internet Site(s)

URL	Description

C. Technologies or Techniques

Type	Description

NHP cellular depletion	Regimen for lymphodepletion with CD4, CD8 monoclonal antibodies and busulfan
NHP ASC transplantation	Process for adipose cell transplant combined with donor bone marrow

D. Inventions, Patent Applications, and/or Licenses

Nothing to Report

E. Other Products

Nothing to report.

VII. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

A. Personnel Efforts

Name (First and Last)	**Institution**	***Role**	**Contribution to the Project**	**Nearest person month worked**	****Non-AFIRM Funding (Y/N)**
Eric A. Elster, MD	USUHS	PI	Oversight of Project, design and review of experiments	1	N
Rolf Barth, MD	UMB	Co-PI	Oversight of Project, design and review of experiments, animal study analysis	1	N
Thomas A. Davis, PhD	UMB	Co-I	Design and review of experiments	1	N
Jeffrey Gimble, MD, PhD	UMB	Post-Doc	Isolation, ex vivo expansion, func characterization and the cryopreservation of non-human primate adipose-de stem cells.	1	N

Other Funding to Support Personnel

Nothing to report.

B. Current Support Changes for the PI, Co-I or Other Senior/Key Personnel

Nothing to Report

Name (First and Last)	Current Support Changes

C. Other Organizational Partners

Nothing to Report.

VIII. Special Reporting Requirements

Nothing to report.

IX. APPENDIX

Abbreviations

ACURO	Animal Care and Use Review Office
ASC	Adipose-Derived Stromal Cells
dBMC	Donor Bone Marrow Cells
HLA	Human Leukocyte Antigen
HRPO	Human Research Protection Office
IRB	Institutional Review Board
MHC	Major Histocompatability Complex
NHP	Non-Human Primate
POD	Post-Operative Day
RTR	Reconstructive Transplant Research
VCA	Vascularized Composite Allograft
VBM	Vascularized Bone Marrow

Adult Tissue-Derived Stem Cells and Tolerance Induction in Nonhuman Primates for Vascularized Composite Allograft Transplantation

Congressionally Directed Medical Research Programs - W81XWH-16-2-0042

PI: Eric Elster, Co-PI Rolf N. Barth **Org:** The Henry Jackson Fdn. for the Advancement of Mil. Med., Inc.

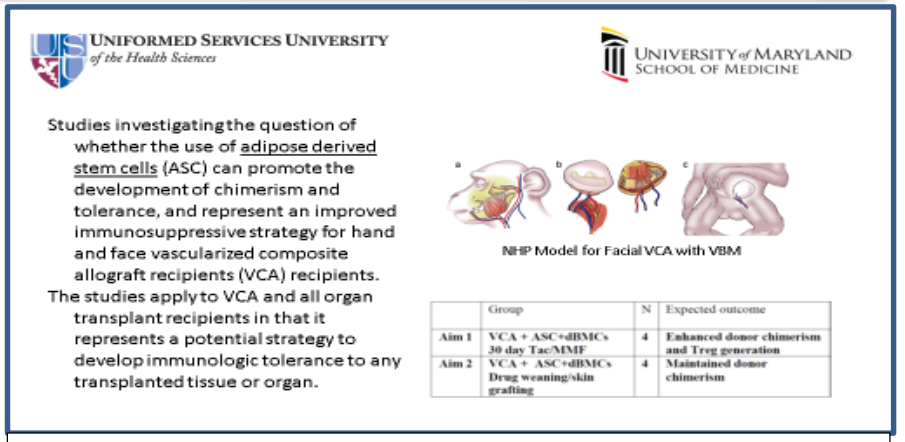
Work Perform at: Uniformed Services Univ. of the Health Sciences/Univ. of Maryland **Award Amount:** 448,415

Study/Product Aim(s)

- Our studies investigate whether utilizing adipose derived stem cells (ASC) in hand/face vascularized composite allograft (VCA) transplants can reduce or eliminate (tolerance) the need for immunosuppressive medications and associated toxicities in service members who would benefit from these reconstructive approaches to devastating facial and limb injuries.
  - Aim 1. To investigate whether ASCs augment chimerism and promote long-term VCA graft survival.
  - Aim 2. To determine whether ASC therapy allows for immunosuppression minimization and development of immunologic tolerance to VCA.

Approach

Non-human primate (NHP) experiments in our established model of facial VCA to examine the ability of ASC establish chimerism, promote graft survival, and establish immunologic tolerance.



Accomplishments: All four (4) maxofacial transplants have been completed ASC/VBM transfusion. The fourth recipient died with 24 hours post surgery due to prolonged anesthesia related complications. We plan to start a 5th VCA transplant during the next report period which provide sufficient data to write a peer-reviewed manuscript.

Timeline and Cost

Activities	FY 16-17	18	19
ASCs augment chimerism in NHP facial VCA	■	■	
ASC therapy allows for immunosuppressive therapy reduction and withdrawal in NHP facial VCA	■	■	
Estimated Budget ($448K)	**0**	**280**	**168**

Milestones/Goals

FY16 Goals

- ✓ Approved UMB IACUC
- ✓ Approved DOD ACURO

FY17 Goals

- ✓ NHP animals screened, selected, and delivered to UMB site
- ✓ Test the immunodepletion/condition strategy in normal NHPs
- ✓ Isolate, ex vivo expand , and functionally characterize NHPs ASCs
- ✓ Develop a biobank of NHP ASCs for in vivo transplantation

FY18-19 Goals

- ✓ completed four partial maxofacial VCA transplants with up to 30-day follow-up
- ✓ Wean graft transplanted NHPs to low level immunosuppression for pending cessation after facial transplant
- ✓ Complete skin grafts and determination of tolerance.
- ✓ Complete follow up data analysis of all NHP VCA experiments

Budget Expenditure to Date:

Actual Expenditure: $444,781.86

Updated: December 13, 2019