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

PRINCIPAL INVESTIGATOR: Gerald Brandacher, MD

CONTRACTING ORGANIZATION: Johns Hopkins University
Baltimore MD 21218

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<p>For many devastating combat and civilian injuries where conventional reconstruction is inadequate, vascularized composite allotransplantation (VCA) has become a viable alternative. However, the toxicities and adverse effects of high dose immunosuppressive drugs have curtailed wider application. Thus the purpose of this project is to develop novel clinically relevant immunosuppression sparing regimens allowing for immunomodulation and tolerance induction after VCA using a translational large animal model. During the current reporting period the group continue to study a belatacept-based protocol to enable calcineurin inhibitor minimization (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). In year 2 of the study, all animals in Aim 1 and 2 have undergone transplantation. 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) have rejected their grafts. 3/5 animals who received belatacept in addition to low dose tacrolimus (group III) have achieved long term graft survival (>230 days). All group IV and V animals that received 60 days of tacrolimus and proceeded to either weaning immunosuppression or transition to belatacept have not shown evidence of rejection thus far. Overall, our preliminary results indicate that belatacept is highly effective as a biologic agent in maintaining allograft survival without the need for conventional high dose calcineurin inhibitor based immunosuppression. Furthermore, the long term graft survival off of immunosuppression for animals treated with low dose tacrolimus suggest that the vascularized bone component of the composite graft may have a robust immunomodulatory effect. Additional clinical follow-up and <i>in vitro</i> experiments are ongoing to characterize the immune status of the current recipients.</p>					
15. SUBJECT TERMS					
Vascularized composite allotransplantation (VCA), Hand transplantation, Face transplantation, Tolerance induction, Immunomodulation, Chimerism, Costimulatory blockade, Belatacept, CTLA4-Ig, Large animal model					
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1. INTRODUCTION

Close to 40% of combat injuries sustained in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) involved severe extremity or craniofacial trauma. Currently, despite the best reconstructive efforts using native tissue, these injuries are not only mutilating, but frequently result in permanent disfigurement and morbidity. For many devastating combat and civilian injuries where conventional reconstruction is inadequate, vascularized composite allotransplantation (VCA) has become a viable alternative. However, the toxicities and adverse effects of the high dose immunosuppressive drugs have curtailed wider application. In particular, the use of calcineurin inhibitors (CNIs, i.e. tacrolimus), currently the mainstay therapy in VCA, is associated with substantial morbidity and is relatively ineffective in preventing antibody mediated injury and chronic rejection.

Thus, the central challenge for VCA is to develop novel treatment concepts to minimize/avoid immunosuppression and extend the benefits of these life-enhancing procedures to the military and civilian patient populations. Biologic agents such as the monoclonal antibody Cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin (CTLA4-Ig) (e.g., abatacept, belatacept), which block T-cell costimulation, have been developed to overcome this limitation, and represent a new paradigm in immunosuppression - biological therapy for maintenance immunosuppression devoid of the toxicities associated with CNIs.

In this study we propose to use the second-generation, FDA approved, CTLA4-Ig belatacept, that has demonstrated potent inhibition of T-cell activation and proven effective in phase II and III trials of kidney transplantation, to develop clinically relevant regimens for immunomodulation and tolerance induction after VCA using a translational large animal model.

2. KEYWORDS

Vascularized Composite allotransplantation (VCA)
Hand transplantation
Face transplantation
Tolerance induction
Immunomodulation
Chimerism
Costimulatory blockade
Belatacept
CTLA4-Ig
Large Animal model

3. ACCOMPLISHMENTS

a. What were the major goals of the project?

The major goals of this project for year 1 (Phase 1) and year 2 (Phase 2) of this project as outlined by the approved statement of work are:

Phase 1, Aim 1: Establish a belatacept-based protocol to enable CNI minimization after VCA.

TASK 1. Obtain institutional Animal Care and Use Committee (ACUC) approval.

TASK 2. Obtain DoD Animal Care and Use Review Office (ACURO) approval

TASK 3. Adapt clinically established induction and CNI maintenance regimen in a fully SLA-mismatched swine hind limb transplantation model.

SUBTASK 1. Perform hind limb transplantation with high-dose TAC maintenance therapy (Group I; n=3)

SUBTASK 2. Perform hind limb transplantation with sub-therapeutic, low-dose TAC treatment (Group II; n=3)

TASK 4. Determine impact of peritransplant belatacept treatment to allow for allograft survival with low-dose (sub-therapeutic) CNI treatment.

SUBTASK 1. Perform hind limb transplantation with low-dose TAC in combination with belatacept (Group III; n=5)

Phase 2, Aim 2: Investigate the possibility to convert from conventional CNI-based immunosuppression to belatacept maintenance with subsequent CNI withdrawal.

TASK 1. Attempt CNI weaning/withdrawal without CTLA4-Ig and assess time course of allograft rejection.

SUBTASK 1. Perform hind limb transplantation with high-dose TAC (60 days) + subsequent TAC weaning (Group IV; n=3)

TASK 2. Repeat CNI weaning/withdrawal protocol with delayed belatacept treatment and maintenance

SUBTASK 1. Perform hind limb transplantation with high-dose TAC (60 days) + late CTLA4-Ig + subsequent TAC weaning and CTLA4-Ig maintenance (Group V; n=5)

b. What was accomplished under these goals?

Phase 1, Aim 1, Year 1: Establish a belatacept-based protocol to enable CNI minimization after VCA.

Aim 1, Tasks 1: Obtain institutional Animal Care and Use Committee (ACUC) approval

Status: Complete; 100%

The specific objectives of this task were met by the approval of the IACUC protocols, allowing the VCA Laboratory to perform the proposed *in-vivo* transplantation experiments.

Aim 1, Task 2: Obtain DoD Animal Care and Use Review Office (ACURO) approval

Status: Complete; 100%

The specific objectives of this task were met by the approval of the ACURO protocols, allowing the VCA Laboratory to perform the proposed *in-vivo* transplantation experiments.

Aim 1, Task 3: Adapt clinically established induction and CNI maintenance regimen in a fully SLA-mismatched swine hind limb transplantation model

Status: Incomplete; 90%

In Phase 1 of the study eleven swine heterotopic hind limb transplants were performed across a full swine leukocyte antigen (SLA-) barrier and animals were enrolled in group 1-3 as outlined by the approved statement of work (SOW) (Table 1). This phase of the study is still ongoing as data acquisition and tissue sampling is not yet completed in Groups 2 & 3.

Table 1: Aim 1 - Experimental Groups

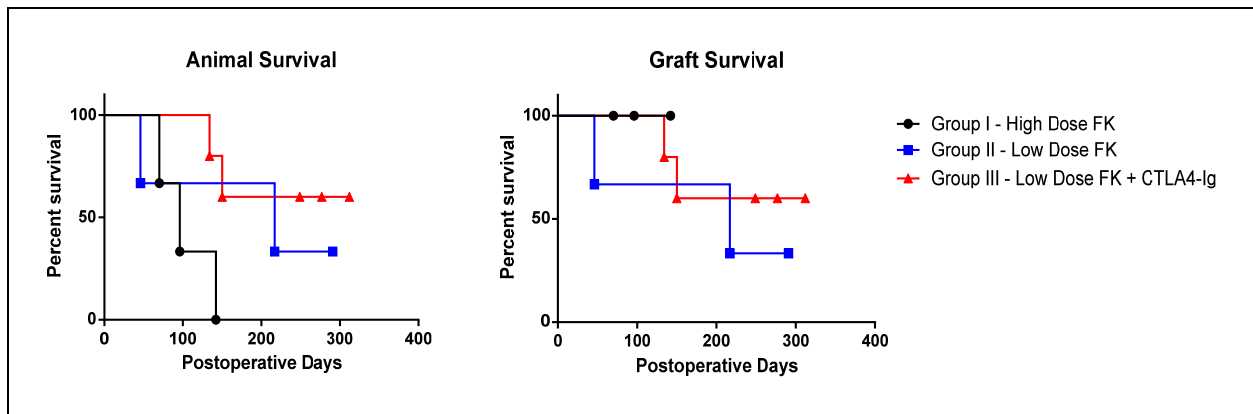
Group	N	SLA Mismatch	Protocol	Rational	Status
I	3	Full	Induction + high-dose TAC maintenance	Control Group: therapeutic CNI	100%
II	3	Full	Induction + low-dose TAC maintenance	Control Group: sub-therapeutic CNI	90%
III	5	Full	Induction + low-dose TAC + CTLA4-Ig maintenance	Experimental Group: Tests role of CTLA4-Ig to allow for graft survival with minimal CNI	90%

Aim 1, Task 3, Subtask 1: Perform hind limb transplantation with high-dose TAC maintenance therapy (Group I; n=3)

All animals in Group 1 (n=3) have undergone heterotopic hind limb allotransplantation.

As hypothesized, high dose tacrolimus (trough level 10-20 ng/mL) has maintained all allografts without clinical signs of rejection throughout the study period (Figure 1). However, in attempting to maintain high dose tacrolimus, it was not uncommon for levels to reach significantly higher trough levels (i.e. 40-60 ng/mL). All three animals died prematurely due to infectious complications associated with high dose immunosuppression. Pig 22312 experienced sudden respiratory arrest and was found to have an airway obstruction from a hyperplastic pharyngeal lymph node. On necropsy, generalized lymphadenopathy was found throughout the animal, including mediastinal and mesenteric lymph nodes. A neutrophilic and histiocytic predominance in the lymph nodes points more towards infection rather than post-transplant lymphoproliferative disease (PTLD). The second premature death in this group, Pig 22227, was due to a gastrointestinal bleed, related to either infectious gastroenteritis/colitis or stress ulcer formation. The third animal, Pig 22229, was euthanized at POD 142 due to infection as well (Figure 1).

Figure 1: Animal and graft survival for animals from subtasks 1.3.1 (Group I, Black), 1.3.2 (Group II, Blue), 1.4.1 (Group III, Red). Note that Group I animals experienced premature deaths due to complications while maintaining allografts without rejection. Group II and III have not experienced premature deaths as tacrolimus levels are kept in a sub-therapeutic range. 2/3 animals in Groups II have rejected their allograft, whereas 3/5 animals in group III have maintained their graft rejection-free long term off of all immunosuppression.



Overall, Group 1 has demonstrated viable heterotopic hind limb allografts while receiving high dose tacrolimus but all three animals died prematurely due to complications associated with significant immunosuppression. These findings support our hypothesis that high dose tacrolimus can maintain vascularized composite allotransplants, but does so at the cost of significant complications.

1.3.2 Aim 1, Task 3, Subtask 2: Perform hind limb transplantation with sub-therapeutic, low-dose TAC treatment (Group II; n=3)

All animals in Group 2 (n=3) have undergone heterotopic hind limb allotransplantation and were maintained on low dose tacrolimus treatment (trough levels 4-6 ng/mL). Pig 22309, upon lowering the dose of tacrolimus to the target range of 4-6 ng/mL, briskly

rejected the graft within 20 days on POD 46 (Figure 2). The first animal from Group 2 demonstrated the inability of low dose tacrolimus (4-6 ng/mL) to maintain the allotransplant and prevent rejection. Pig 22573 did not demonstrate overt evidence of rejection until POD 191 and was euthanized at POD 217 when it reached grade IV rejection. Interestingly, Pig 22545 has achieved long term graft survival to POD 291 with only low dose tacrolimus immunosuppression for 150 days post-transplant (Figure 3). This observation was unexpected and may be explained by the immunomodulatory effect of the transplanted donor bone marrow niche carried by the vascularized bone component of the composite graft. Further characterization of donor specific unresponsiveness using in-vitro techniques such as mixed lymphocyte reactions are underway and results are expected to be available during the upcoming two quarterly reports.

Figure 2. Clinical and histologic images of an example of graft rejection in pig 22309 on POD 46. A.) Clinical image of complete epidermal necrosis. B.) Histologic image of skin biopsy from the graft demonstrating severe mononuclear cell infiltrate with loss of epidermal and dermal junction. C.) Muscle biopsy showing minimal inflammatory infiltrates indicating that the strong reactive response against skin is not present in other parts of the composite allograft.

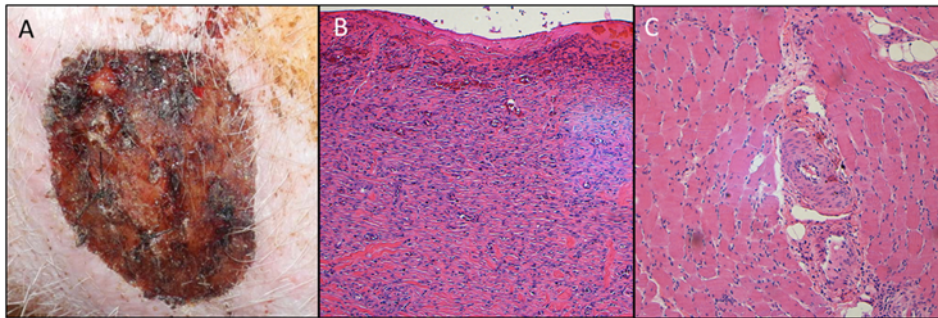


Figure 3: Clinical images of allografts from long-term graft survival animals in subtask 1.3.2 and 1.4.1. Pig 22545 is in group II and has received low dose tacrolimus until POD 150 and currently has no signs of rejection while being off of all immunosuppression. Pig 22570, 22575 and 22590 received belatacept in addition to low dose tacrolimus until POD 150 and have all achieved long-term rejection free graft survival.



Aim 1, Task 4: Determine impact of peritransplant belatacept treatment to allow for allograft survival with low-dose (sub-therapeutic) CNI treatment

Aim 1, Task 4, Subtask 1: Perform hind limb transplantation with low-dose TAC in combination with belatacept (Group III; n=5)

All animals in Group 3 (n=5) have undergone heterotopic hind limb allotransplantation and were maintained on low dose tacrolimus treatment (4-6 ng/mL) along with intermittent belatacept infusion administered on POD 2, 7, 14, 30, 60, 90, 120, 150. Two animals (Pig 22575 and 22571) rejected their graft at POD 150 and POD 134, respectively (Figure 1). The other three animals in this group all achieved long-term graft survival (>230 days) despite cessation of all immunosuppressive agents by POD150 (Figure 3). These results are very encouraging and suggest the potential efficacy of our induction regimen with belatacept in conjunction with low dose Tacrolimus, thereby avoiding the complications of high dose CNI. Long-term survival of all components of the vascularized composite allograft has not been previously demonstrated with this regimen in a large animal model. Further mechanistic studies are underway to attempt to elucidate the role of the donor vascularized bone marrow niche present from the transplanted lower extremity long bones.

Phase 2, Aim 2: Investigate the possibility to convert from conventional CNI-based immunosuppression to belatacept maintenance with subsequent CNI withdrawal.

Status: Incomplete; 90%

In Phase 2 of the study eight swine heterotopic hind limb transplants were performed across a full swine leukocyte antigen (SLA-) barrier and animals were enrolled in group 4 & 5 as outlined by the approved statement of work (SOW) (Table 2). This phase of the study is still ongoing as data acquisition and tissue sampling is not yet completed.

Table 2: Aim 2 – Experimental Groups

Group	N	SLA Mismatch	Protocol	Rational	Status
IV	3	Full	Induction + high-dose TAC (60 days) + Subsequent TAC weaning	Control Group: CNI weaning without CTLA4-Ig	90%
V	5	Full	Induction + high-dose TAC (60 days) + late CTLA4-Ig + Subsequent TAC weaning and CTLA4-Ig maintenance	Experimental Group: Investigate the ability to wean/withdraw CNIs after delayed CTLA4-Ig treatment and maintenance	90%

2.1 Aim 2, Task 1: Attempt CNI weaning/withdrawal without CTLA4-Ig and assess time course of allograft rejection.

All animals in group IV (n=3) have undergone heterotopic hind limb allotransplantation. All animals in this group have been weaned off of CNI and are currently not on any immunosuppression (Figure 4). Thus far, all animals are beyond POD 190 without evidence of graft rejection (Figure 5). In contrast to group I animals that received high dose tacrolimus for 150 days and were complicated by significant infectious complications, group IV animals have not demonstrated significant toxicity from their peritransplant tacrolimus therapy. This may be in part explained by the shorter course of therapy and the improved maintenance of tacrolimus trough within the target range of (10-20 ng/mL) (Figure 6). Overall, contrary to our initial hypothesis, group IV animals have not rejected their allograft soon after weaning of CNI. These findings correlate well with our previous findings that the vascularized bone marrow component contained within the VCA may exert potent immunomodulatory effects. This group is therefore still ongoing as additional clinical follow-up and immunologic assays will be performed to elucidate the underlying immunoregulatory mechanisms in this group.

Figure 4. Animal and graft survival curves for animals from subtasks 2.1.1 (Group IV, Orange) and 2.2.1 (Group V, Green): high dose tacrolimus (15-20 ng/mL) for 60 days ceased or transitioned to intermittent belatacept, respectively. Note none of the animal have died prematurely or rejected (Grade IV) their grafts.

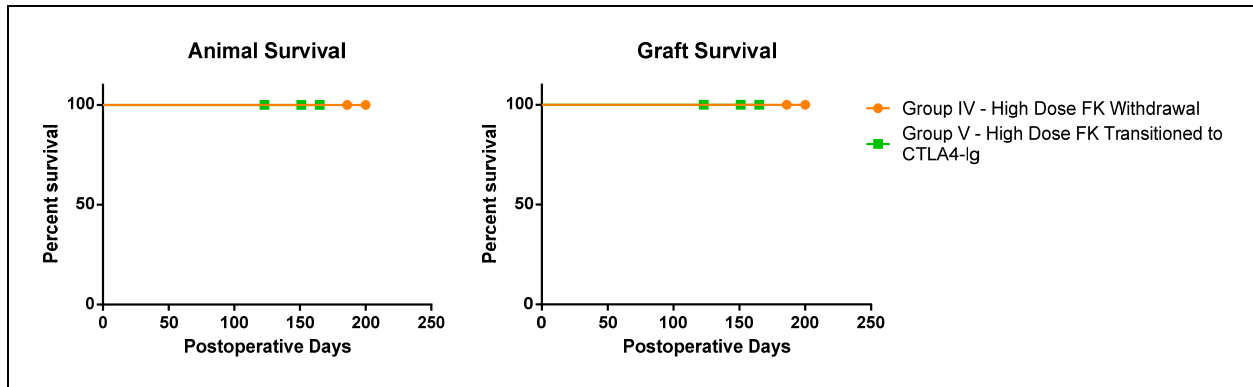


Figure 5: Clinical images of allografts from animals in subtask 2.1: high dose tacrolimus for 60 days followed by withdrawal of immunosuppression. All three animals have been off of tacrolimus since POD 60 and have not demonstrated evidence of rejection.

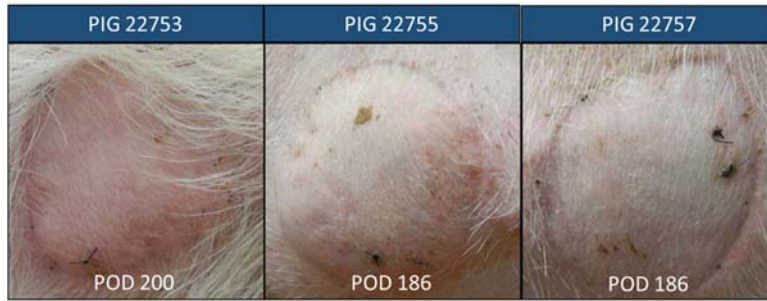
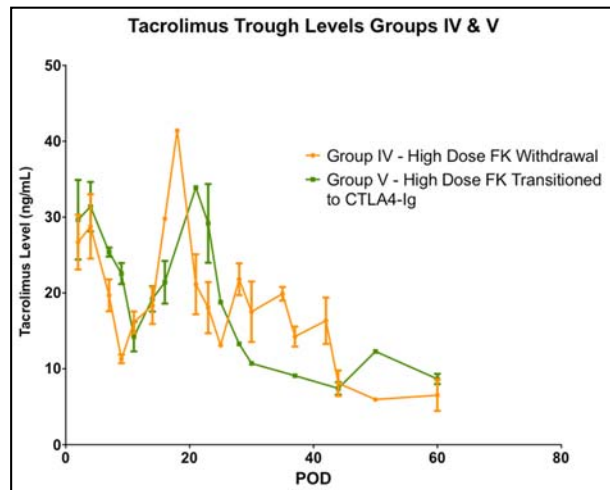


Figure 6: Mean tacrolimus trough levels with standard deviation error bars for animals from subtask 2.1.1 (Group IV, Orange) and 2.2.1 (Group V, Green): high dose tacrolimus (15-20 ng/mL) for 60 days ceased or transitioned to intermittent belatacept, respectively. Note that both groups have similar trends, with high levels for 30 days, which are then gradually weaned and discontinued by POD 60.

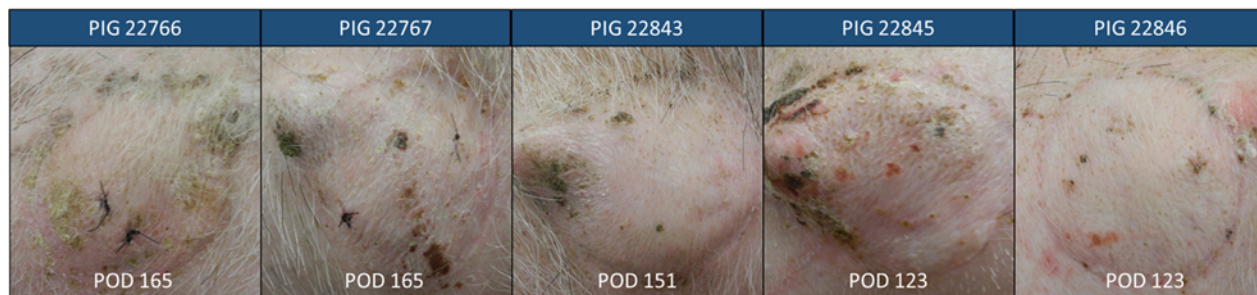


2.2 Aim 2, Task 2: Repeat CN1 weaning/withdrawal protocol with delayed belatacept treatment and maintenance

All animals in group V (n=5) have undergone heterotopic hind limb allotransplantation and have been weaned off of CN1 on POD60 and transitioned to belatacept maintenance (Figure 3). All animals have completed their course of belatacept maintenance. No active rejection has been noted thus far in accordance with our hypothesis that CN1 based immunosuppression can be transitioned to belatacept maintenance (Figure 7). Furthermore, no additional toxicities have been noted in this group with the addition of belatacept treatment. This group is still ongoing as additional clinical follow-up and immunologic assays will be performed for animals in this group.

Figure 7: Clinical images of allografts from animals in subtask 2.2: high dose tacrolimus for 60 days followed by transition to belatacept maintenance until POD 150. 3/5 animals have completed the treatment period, and no animal has shown clinical rejection of their grafts. Note that scabbed and erythematous

areas on pigs 22845 are due to trauma to grafts and not rejection (animals have tendency to rub grafts on cages).



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

All co-investigators involved in the project have received training in *in-vivo* and *in-vitro* aspects related to the study. Performing the heterotopic hind limb allotransplants is a complex endeavor requiring expertise in surgical principles, microvascular surgery, and transplant surgery. Preoperative planning and coordination is paramount to success, as well as diligent postoperative care of the animals. Moreover, all co-investigators are gaining knowledge and abilities to manage a complex translational large animal project under supervision of the PI.

Professional development is provided during weekly project updates and laboratory meetings, requiring careful preparation of weekly activities and future plans. Preparation for these presentations to the study group fosters the skill to communicate effectively the details and rationale of the project to other laboratory members. Furthermore, presentations of the results from this study in local and national formats by study group members have further developed young scientist's communication skills.

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

An abstract detailing the findings from all animals included in Aim 1 was presented at the International Hand and Composite Tissue Allotransplantation Society (IHCTAS) Annual Meeting on April 16th, 2015.

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

In the next reporting period we plan to begin transplants for Groups VI and VIII with the goal to complete all transplants for Aim 3 animals within the next six months period. For animals in Aim 1 that have achieved long term graft survival, we are currently in the process of performing *in-vitro* mixed-lymphocyte reactions to determine whether donor

specific tolerance has been achieved. Aim 2 animals will be monitored clinically for evidence of rejection, and *in-vitro* assays will be performed with collected samples.

4. IMPACT:

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

Our preliminary results are highly encouraging and indicate that CTLA4-Ig has the ability to both allow for CNI minimization after VCA as well as to maintain rejection free allograft survival after weaning and complete withdrawal of CNI in patients who have already undergone VCA. This could allow to develop 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. Furthermore, the inclusion of vascularized bone in our model appears to have an additional immunomodulatory effect as evidenced by the long-term survival of grafts with low dose immunosuppression. Additional clinical follow-up and *in vitro* assays need to be performed to characterize this finding.

b. What was the impact on other disciplines?

Nothing to report

c. What was the impact on technology transfer?

Nothing to report

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

Nothing to report

5. 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

There are no current problems or issues to report. Our irradiation induction protocol, surgical technique and postoperative management protocol have all been optimized and successfully implemented in the past year. We have completed all transplants as planned in the original SOW.

c. Changes that had a significant impact on expenditures

Our rate of expenditure has increased from the previous annual report as we have performed a significant number of transplants along with the postoperative treatment regimen (primarily belatacept). Furthermore, *in-vitro* analysis is fully underway and the cost of reagents will be expected to increase in the upcoming year. In addition, due to the encouraging long-term survival outcomes housing costs have been higher than initially anticipated.

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

Nothing to report

e. Significant changes in use or care of human subjects

Nothing to report

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

Nothing to report

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

Nothing to report

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name: Gerald Brandacher

Project Role: Principal Investigator

Nearest Person Month Worked: 10%

Contribution to Project: Dr. Brandacher oversees all aspects of project planning, execution and data analysis. He actively participated in all animal surgeries.

Funding Support: Grant

Name: W. P. Andrew Lee

Project Role: Co-Investigator

Nearest Person Month Worked: 2%

Contribution to Project: Dr. Lee participated in project planning and data analysis.

Funding Support: Departmental Sources

Name: Justin Sacks

Project Role: Co-Investigator

Nearest Person Month Worked: 5%

Contribution to Project: Dr. Sacks participated in all donor surgeries.

Funding Support: Departmental Sources

Name: Jaimie Shores

Project Role: Co-Investigator

Nearest Person Month Worked: 5%

Contribution to Project: Dr. Shores participated in all recipient surgeries.

Funding Support: Departmental Sources

Name: Damon Cooney

Project Role: Co-Investigator

Nearest Person Month Worked: 5%

Contribution to Project: Dr. Cooney participated in all recipient surgeries, post-transplant care and data analysis.

Funding Support: Departmental Sources

Name: Howard Wang

Project Role: Post-Doctoral Fellow

Nearest Person Month Worked: 50%

Contribution to Project: Dr. Wang participated in all recipient surgeries, pre and post-transplant care, performed *in vitro* assays and data analysis.

Funding Support: Grant

Name: Ned Swanson

Project Role: Post-Doctoral Fellow

Nearest Person Month Worked: 50%

Contribution to Project: Dr. Swanson participated in all recipient surgeries, pre and post-transplant care, performed *in vitro* assays and data analysis.

Funding Support: Grant

Name: BC Oh

Project Role: Lab Technician

Nearest Person Month Worked: 25%

Contribution to Project: Dr. Oh participated in all recipient surgeries, pre and post-transplant care, performed *in vitro* assays and data analysis.

Funding Support: Grant

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

i. Organization Name: Massachusetts General Hospital

ii. Location of Organization: Boston, MA

Massachusetts General Hospital provided support and consultation with regard to donor/recipient selection and matching as well as post-transplant immunological *in vitro* assays.

8. SPECIAL REPORTING REQUIREMENTS

a. **QUAD CHARTS:** Attached.

9. APPENDICES

Nothing to report.

Immunomodulation and Tolerance Induction after VCA Using Biologic Agents (CTLA4-Ig) and Donor Bone Marrow Cells

MR120034P10, Restorative Transplantation Research

Award Number: W81XWH-13-2-0060

PI: Gerald Brandacher, M.D.

Org: Johns Hopkins University School of Medicine Award Amount: \$1,297,034



Study/Product Aim(s)

- Establish a belatacept-based protocol to enable CNI minimization after Vascularized Composite Allograft Transplantation (VCA).
- Investigate the possibility to convert from conventional CNI-based immunosuppression to belatacept maintenance with subsequent CNI withdrawal.
- Compare immunomodulatory donor bone marrow (BM) infusion (BMI) to BM transplantation (BMT) with establishment of durable mixed chimerism for induction of tolerance and/or VCA survival on CNI-free immunosuppression using a belatacept-based regimen.

Approach

In this study we propose to develop novel protocols using donor bone marrow cells and FDA-approved biologic agents (Cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin [CTLA4-Ig], belatacept) for the induction of immune tolerance with minimal or only transient immunosuppression in de-novo VCA recipients and to allow withdrawal of calcineurin inhibitors (CNIs) from patients that have already been transplanted under conventional immunosuppression. Studies will be performed using a translational large animal model for VCA as outlined in Figure 1.

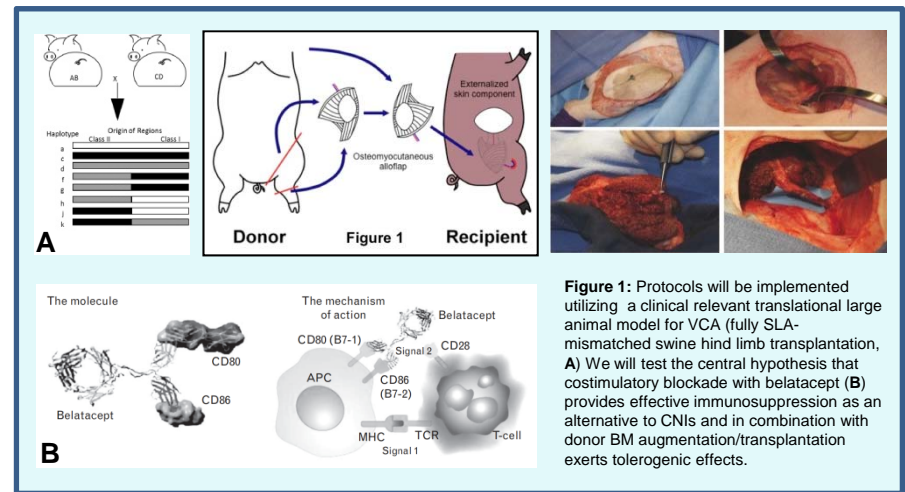


Figure 1: Protocols will be implemented utilizing a clinical relevant translational large animal model for VCA (fully SLA-mismatched swine hind limb transplantation, **A**) We will test the central hypothesis that costimulatory blockade with belatacept (**B**) provides effective immunosuppression as an alternative to CNIs and in combination with donor BM augmentation/transplantation exerts tolerogenic effects.

Accomplishment: Implemented successfully first clinical protocol for upper extremity transplantation using donor bone marrow cell therapies and tacrolimus monotherapy.

Timeline and Cost

Activities	CY	14	15	16
Establish a belatacept-based protocol to enable CNI minimization after VCA (JHU)		█		
Test ability to convert from conventional CNI-based immunosuppression to belatacept maintenance with subsequent CNI withdrawal (JHU)			█	
Use BMI combined with CNI-free belatacept-based regimen to establish chimerism and tolerance induction after VCA (JHU)			█	█
Use BMT combined with CNI-free belatacept-based regimen to establish chimerism and tolerance induction after VCA (MGH)				█
Estimated Budget (\$K)		\$379,907	\$366,875	\$633,096

Updated: (10/15/2015)

Goals/Milestones

CY14 Goals – CNI minimization

- ✓ Adapt clinically established induction and CNI maintenance regimen in this translational large animal VCA model
- ✓ Determine impact of peri-transplant belatacept treatment to allow for allograft survival with low-dose CNI treatment

CY15 Goals – CNI withdrawal

- ✓ Attempt CNI weaning/withdrawal without CTLA4-Ig and assess time course of allograft rejection
- ✓ Perform CNI weaning/withdrawal with delayed belatacept treatment and maintenance

CY16 Goals – CNI free immunosuppression and tolerance induction

- Determine impact of BMI vs. BMT combined with short-term CNI on immunomodulation and allograft survival
- Develop tolerance protocol combining optimized BM regimen with short-course CNI and peri-transplant belatacept treatment
- Develop tolerance protocol combining optimized BM regimen with short-term CNI, peri-transplant and short course post-transplant belatacept treatment

Comments/Challenges/Issues/Concerns

- Experiments as outlined by SOW are in progress, validation and adaptation of induction regimen completed

Budget Expenditure to Date

Projected Expenditure: NA

Actual Expenditure: \$841,654