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TITLE: Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy

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14. ABSTRACT Recent improvements in body armor have reduced the rate of combat death but increased the rate of extremity injury, burn and limb loss in surviving casualties. As such, methods to replace injured limbs are increasingly required to support combat service personnel. Vascularized composite all transplantation (VCA) has recently emerged as a promising strategy for the repair or replacement of amputated limbs, and novel methods for immune management to prevent the rejection of transplanted tissues are now available that may greatly reduce the risks associated with limb transplantation.					
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I. Introduction

Recent improvements in body armor have reduced the rate of combat death but increased the rate of extremity injury, burn and limb loss in surviving casualties. As such, methods to replace injured limbs are increasingly required to support combat service personnel. Vascularized composite allotransplantation (VCA) has recently emerged as a promising strategy for the repair or replacement of amputated limbs, and novel methods for immune management to prevent the rejection of transplanted tissues are now available that may greatly reduce the risks associated with limb transplantation.

The proposal will utilize a comprehensive approach to efficiently apply the newest clinically proven methods of modulation of the immune system to lower the risk and improve the benefits of patients after limb reconstruction through transplantation. The study provides a new platform to optimize integration of a limb after limb loss with a therapy based on a once a month medication. The entire study addresses the increase clinical need of limb loss seen in the current combat conflicts. The intervention provides the reconstruction of skin, muscle, tendon, bone, nerve, and vessels as a functional unit (limb) in individuals who suffered limb loss. The treatment includes the newest medication recently

approved by the US Food and Drug Administration. Studies will define the efficacy of the newest medication on protective immunity and the mechanisms of graft rejection. Additionally, the studies will be conducted concurrently to determine in objective terms the integration of the recipients use of their transplanted limb compared to their pre-transplant state. Moreover, evaluation of the recipient's quality of life will be performed.

II. Body

Task 1. : To use an efficacious immunomodulation regimen based on belatacept to optimize the integration of limb transplantation after limb loss.

Regulatory Review and Approval Process

During this reporting period we completed the submission of the Investigational New Drug/Investigational Device Exemption to the US FDA. Approval was granted for the use of Belatacept {IND 113,206, Nulojix (Belatacept)}

Clinical Trial

Our studies are under an Institutional Review Board (IRB) approved protocol entitled "Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy".

During this reporting period we submitted the protocol to the Emory IRB and HRPO. The IRB granted full approval of the protocol on October 23, 2013. The proposal was subsequently submitted to HRPO. The protocol was reviewed by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, US Army, and USAMRMC human subjects protection requirements on November 5, 2013.

During the next reporting period we plan to continue with the screening of potential candidates for limb transplantation. A potential problem area in the next phase of the study will be recruitment. For that purpose, we submitted recruitment letters and documents, which were approved by both the IRB and HRPO. We intent to distribute the approved documents to DoD and Civilian centers nation-wide. We also plan to complete the registration of the study at Grants.gov for website access.

III. Research Accomplishments

- a. Approval of the IND 113,206, Nulojix (Belatacept). Sponsor: Linda C. Cendales, MD
- b. Approval of the study protocol "Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy" by the Emory IRB and US Army Medical Research and Materiel Command (USAMRMC), Office of

Research Protections (ORP), Human Research Protection
Office (HRPO)

IV. Reportable outcomes

N/A to this study period

V. Conclusion

This entire study addresses the increase clinical need of limb loss seen in the current combat conflicts. The intervention provides the reconstruction of skin, muscle, tendon, bone, nerve, and vessels as a functional unit (limb) in individuals who suffered limb loss.