MEMORANDUM FOR SGVT  
ATTN: LT COL MICHAEL R DAVIS

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval


2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are 59 MDW staff member, we can forward your request for funds to the designated wing POC.

4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

LINDA STEEL-GOODWIN, Col, USAF, BSC  
Director, Clinical Investigations & Research Support

*Partners in a high-performance health system, dedicated to excellence in global care*
Vascularized Composite Allotransplantation (VCA) in Swine (Sus scrofa) for Optimization of Reconstruction of Battlefield Injuries Using the Locally Applied enzyme activated tacrolimus eluting hydrogels significantly delay the onset of acute rejection of VCA grafts.

10. IS THIS MATERIAL SUBJECT TO ANY LEGAL RESTRICTIONS FOR PUBLICATION OR PRESENTATION THROUGH A COLLABORATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA), MATERIAL TRANSFER AGREEMENT (MTA), INTELLECTUAL PROPERTY RIGHTS AGREEMENT ETC.?  
  □ YES  ☑ NO  NOTE: If the answer is YES then attach a copy of the Agreement to the Publications/Presentations Request Form.

11b. PUBLISHED ABSTRACT (List intended publication/journal.)

☐ 11c. FOSTER (To be demonstrated at meeting; name of meeting, city, state, and date of meeting.)

☒ 11d. PLATFORM PRESENTATION (At civilian institutions name of meeting, state, and date of meeting)

2016 Society of Military Surgeons, Boston MA 11-14 March 2016

☐ 11e. OTHER (Describe name of meeting, city, state, and date of meeting.)

12. EXPECTED DATE WHEN YOU WILL NEED THE CRD TO SUBMIT YOUR CLEARED PRESENTATION/PUBLICATION TO DTIC.

NOTE: All publications/presentations are required to be placed in the Defense Technical Information Center (DTIC).

DATE:
March 18, 2016

13. 59 MDW PRIMARY POINT OF CONTACT (Last Name, First Name, M.I., email):
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15. AUTHORSHIP AND CO-AUTHOR(S) List in order they will appear in the manuscript.

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17. AUTHOR'S SIGNATURE:

18. DATE:
15 Mar 2016

19. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE:
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20. APPROVING AUTHORITY'S SIGNATURE:

21. DATE:
15 Mar 2016
Slide presentation includes disclaimer required by the JointEthics Regulation. There are no ethics issues with making this presentation at the 2016 Society of Military Surgeons Meeting.
Locally applied enzyme activated tacrolimus eluting hydrogels significantly delay the onset of acute rejection of VCA grafts

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General Surgery Resident, US Army Institute of Surgical Research,
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Disclaimer

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of Defense.

The experiments reported herein were conducted according to the principles set forth in the National Institute of Health Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966, as amended.
Impact of Military Trauma Care and Research

Injury Severity Score

Case Fatality Rate - Afghanistan

Case Fatality Rate
New rung on the reconstructive ladder

- Vascularized composite allotransplantation
- Free tissue transfer, e.g., latissimus dorsi flap
- Regional flaps, e.g., posterior interosseous
- Local flap, e.g., rotational/transposition
- Skin graft
- Secondary closure
- Primary closure
Vascularized Composite Allotransplantation (VCA)

- Multiple types of tissues are transplanted as a single functional unit
- Replaces like with like and restores form and function
- Eliminates autologous donor site morbidity and minimizes the need for multiple reconstructive procedures
Vascularized Composite Allotransplantation (VCA)

- Current challenges and limitations
  - A life-enhancing but not a life-saving procedure
  - Requires lifelong systemic immunosuppression
    - Opportunistic infections: 88%
    - Metabolic complications: 70%
    - $\geq 1$ episode of acute rejection within 1st year: 85%
  - Limited to highly motivated patients
  - Limited donor pool

Background

- A novel model of VCA

- Evaluation of a drug eluting hydrogel
A New Model

- Small animal models are technically challenging and lack immunologic maturity
- Previous orthotopic models in non-human primates and canines are no longer in use
- Currently only heterotopic swine models exist


A New Model

- Ethically acceptable
- Reproducible
- Genetically controlled animals
- Orthotopic model to assess functionality
- Evaluation of bone, tendon and nerve healing
Anatomy
Anatomy

A – Axillary Artery
B – Radial Artery
C – Interosseous Branch (of Fries)
D – Median Artery
E – The Nest (of Lawson)

VA – Vascular Anastomosis
Ost – Osteotomy Site
Enzyme Activated Drug Eluting Hydrogel

RESEARCH ARTICLE

TRANSPLANTATION

A single localized dose of enzyme-responsive hydrogel improves long-term survival of a vascularized composite allograft

Thusitha Gajanayake,¹,²* Radu Olariu,¹,²* Franck M. Leclère,¹,² Ashish Dhayani,³ Zijiang Yang,⁴ Anjan K. Bongoni,²,⁵ Yara Banz,⁶ Mihai A. Constantinescu,¹,² Jeffrey M. Karp,⁴† Praveen Kumar Vemula,³† Robert Rieben,²† Esther Vögelin¹,²

Currently, systemic immunosuppression is used in vascularized composite allotransplantation (VCA). This treatment has considerable side effects and reduces the quality of life of VCA recipients. We loaded the immunosuppressive drug tacrolimus into a self-assembled hydrogel, which releases the drug in response to proteolytic enzymes that are overexpressed during inflammation. A one-time local injection of the tacrolimus-laden hydrogel significantly prolonged graft survival in a Brown Norway–to–Lewis rat hindlimb transplantation model, leading to a median graft survival of >100 days compared to 33.5 days in tacrolimus only–treated recipients. Control groups with no treatment or hydrogel only showed a graft survival of 11 days. Histopathological evaluation, including anti-graft antibodies and complement C3, revealed significantly reduced immune responses in the tacrolimus-hydrogel group compared with tacrolimus only. In conclusion, a single-dose local injection of an enzyme-responsive tacrolimus-hydrogel is capable of preventing VCA rejection for >100 days in a rat model and may offer a new approach for immunosuppression in VCA.
Methods

- Three groups
  - Group 1: Controls – no immunosuppression
  - Group 2: High dose tacrolimus eluting hydrogel (84mg)
  - Group 3: Low dose tacrolimus eluting hydrogel (49mg)
- 1 swine leukocyte antigen (SLA) donor-recipient mismatch
- No systemic immunosuppression
- Hydrogel injected in the subcutaneous layer following revascularization
- AST, LDH, CK, TNF-a, IL-6, myoglobin, and biopsies were assessed for signs of systemic toxicity and/or acute rejection
- End-point – Banff grade 4 acute rejection or 100 days
Results

Rejection against time of allografts

- Control
- High dose Tac
- Low dose Tac
- POD2 Death
- Failure of revascularization

Grade of rejection vs. Time / post op days
Results

Tacrolimus systemic levels

Time in days post transplantation

tacrolimus in ng/ml
Conclusions

- The orthotopic model of swine VCA is an optimal model for investigating novel immunologic strategies.
- Hydrogels are able to delay the onset of acute rejection with no gross safety concerns and without clinically detectable systemic levels of tacrolimus.
Future direction

- Further hydrogel protocols to establish optimal dosing regimen and potential protocols for re-loading hydrogels

- Increased survival duration to evaluate longer term rejection and side effects profile
Thank you

USAISR/59MDW
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Lt Col Dmitry Tuder
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CPT Lin Wang
Mr Raul Corpus

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