



DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
LACKLAND AIR FORCE BASE TEXAS

18 MAR 2016

MEMORANDUM FOR SGVT

ATTN: LT COL MICHAEL R DAVIS

FROM: 59 MDW/SGVU

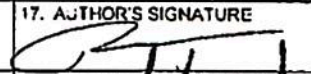

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Hydrogen Sulfide Delays Onset of Acute Rejection in a Porcine VCA Model** presented at **2016 Society of Military Surgeons, Boston, MA, 17-19 March 2016** with MDWI 41-108, and has been assigned local file #**16136**.
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

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

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1. TO CLINICAL RESEARCH	2. FROM: (Author's Name, Rank, Grade, Office Symbol) Michael R Davis, O-6, Lt Col, 59MDW ST	3. GME/GHSE STUDENT: <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	4. PROTOCOL NUMBER: Navy 15-09
5. PROTOCOL TITLE: (NOTE: For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.) Vascularized Composite Allotransplantation (VCA) in Swine (Sus scrofa) for Optimization of Reconstruction of Battlefield Injuries Using the			
6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED: Hydrogen Sulfide Delays Onset of Acute Rejection in a Porcine VCA Model			
7. FUNDING RECEIVED FOR THIS STUDY? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO FUNDING SOURCE: 59MDW ST			
8. DO YOU NEED FUNDING SUPPORT FOR PUBLICATION PURPOSES: <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO			
9. IS THIS MATERIAL CLASSIFIED? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO			
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.? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO NOTE: If the answer is YES then attach a copy of the Agreement to the Publications/Presentations Request Form.			
11. MATERIAL IS FOR: <input checked="" type="checkbox"/> DOMESTIC RELEASE <input type="checkbox"/> FOREIGN RELEASE CHECK APPROPRIATE BOX OR BOXES FOR APPROVAL WITH THIS REQUEST. ATTACH COPY OF MATERIAL TO BE PUBLISHED/PRESENTED.			
<input type="checkbox"/> 11a. PUBLICATION/JOURNAL (List intended publication/journal.)			
<input type="checkbox"/> 11b. PUBLISHED ABSTRACT (List intended journal.)			
<input type="checkbox"/> 11c. POSTER (To be demonstrated at meeting: name of meeting, city, state, and date of meeting.)			
<input checked="" type="checkbox"/> 11d. PLATFORM PRESENTATION (All civilian institutions: name of meeting, state, and date of meeting.) 2016 Society of Military Surgeons, Boston MA 17-10, Mar 2016			
<input type="checkbox"/> 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) Corpus, Raul S raul.s.corpus.ctr@mail.mil			14. DUTY PHONE/PAGER NUMBER 210.539.4404
15. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.			
a. LAST NAME, FIRST NAME AND M.I.	GRADE/RANK	SQUADRON/GROUP/OFFICE SYMBOL	INSTITUTION (if not 59 MDW)
Primary/Corresponding Author Fries Charles A	O-4	59MDW ST	
b. Lawson Shari D	VOI.	59MDW ST	
c. Wang Lin C	O-3	59MDW ST	
d. Villamarin Carole Y	O-3	59MDW ST	
e. Gorantla Vijay	VOI.	59MDW ST	
f. Davis Michael R	O-5	59MDW ST	
I CERTIFY ANY HUMAN OR ANIMAL RESEARCH RELATED STUDIES WERE APPROVED AND PERFORMED IN STRICT ACCORDANCE WITH 32 CFR 219, AFMAN 40-401, IP, AND 59 MDW 41-108. I HAVE READ THE FINAL VERSION OF THE ATTACHED MATERIAL AND CERTIFY THAT IT IS AN ACCURATE MANUSCRIPT FOR PUBLICATION AND/OR PRESENTATION.			
16. AUTHOR'S PRINTED NAME, RANK, GRADE Charles A Fries, O-4		17. AUTHOR'S SIGNATURE <i>for</i> 	18. DATE 15 MAR 2016
19. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE Michael R. Davis, O-5, Director RESTOR, Deputy Commander, USA		20. APPROVING AUTHORITY'S SIGNATURE 	21. DATE 15 MAR 2016

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS		
1st ENDORSEMENT (59 MDW/SGVU Use Only)		
TO: Clinical Research Division 59 MDW/CRO Contact 292-7141 for email instructions	22. DATE RECEIVED <i>16 Mar 16</i>	23. ASSIGNED PROCESSING REQUEST FILE NUMBER <i>161-16</i>
24. DATE REVIEWED	25. DATE FORWARDED TO 502 ISG/JAC	
26. AUTHOR CONTACTED FOR RECOMMENDED OR NECESSARY CHANGES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES If yes, give date: _____ <input type="checkbox"/> N/A		
27. COMMENTS <input checked="" type="checkbox"/> APPROVED <input type="checkbox"/> DISAPPROVED		
28. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER <i>Linda D. Harris, GS-14 Chief, Ops Br</i>	29. REVIEWER SIGNATURE <i>Linda D Harris</i>	30. DATE <i>16 Mar 16</i>
2nd ENDORSEMENT (502 ISG/JAC Use Only)		
31. DATE RECEIVED	32. DATE FORWARDED TO 59 MDW/WPA	
33. COMMENTS <input checked="" type="checkbox"/> APPROVED (In compliance with security and policy review directives) <input type="checkbox"/> DISAPPROVED Slide presentation includes the disclaimer required by the Joint Ethics Regulation. There are no ethics issues with making this presentation at the 2016 Society for Military surgeons meeting.		
34. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER <i>Holly J. Mackey, GS-13</i>	35. REVIEWER SIGNATURE <i>Holly J Mackey</i>	36. DATE <i>16 Mar 2016</i>
3rd ENDORSEMENT (59 MDW/WPA Use Only)		
37. DATE RECEIVED 17 March 2016	38. DATE FORWARDED TO 59 MDW/SGVU 18 March 2016	
39. COMMENTS <input checked="" type="checkbox"/> APPROVED (In compliance with security and policy review directives) <input type="checkbox"/> DISAPPROVED		
40. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER Christopher Carwile, TSgt/E-6, NCOIC, PA	41. REVIEWER SIGNATURE CARWILE CHRISTOPHER STEWART 128047229 <small>Do not sign by CARWILE CHRISTOPHER STEWART 128047229 OR 5902 1618 00000000 000000 000000 #CARWILE CHRISTOPHER STEWART 128047229 Date: 20160318 10:31:43 -0500</small>	42. DATE 18 March 2016
4th ENDORSEMENT (59 MDW/SGVU Use Only)		
43. DATE RECEIVED	44. SENIOR AUTHOR NOTIFIED BY PHONE OF APPROVAL OR DISAPPROVAL <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> COULD NOT BE REACHED <input type="checkbox"/> LEFT MESSAGE	
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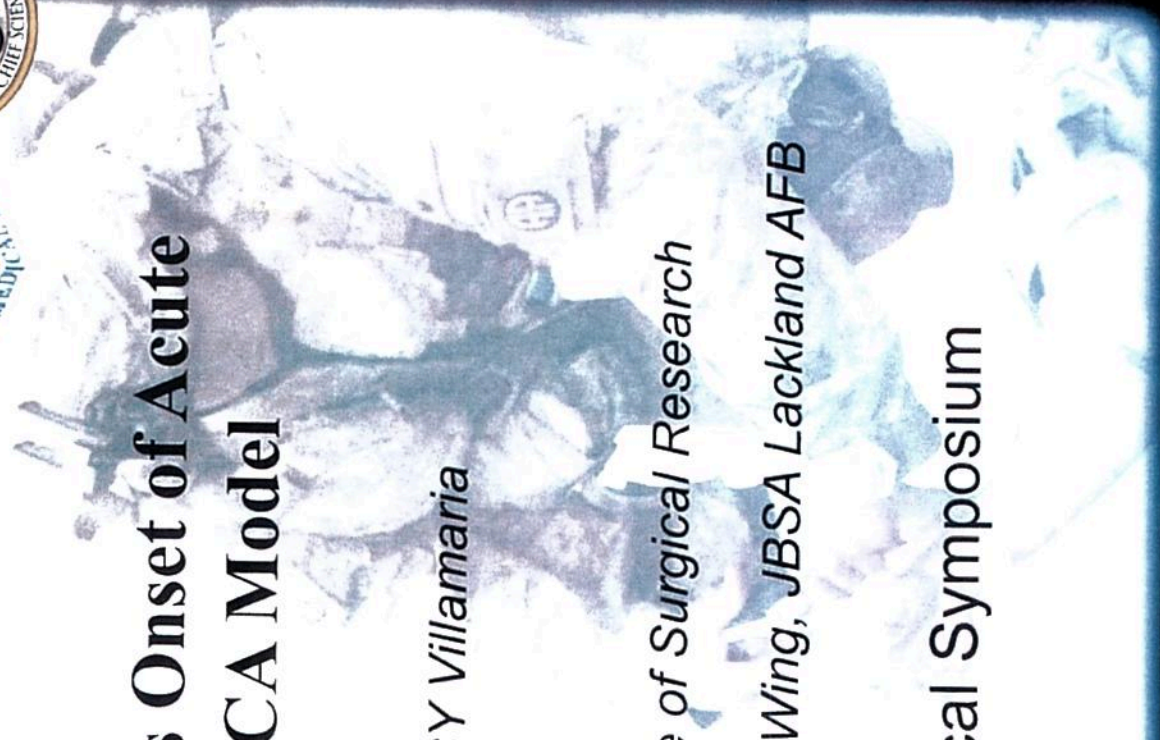
Hydrogen Sulfide Delays Onset of Acute Rejection in a Porcine VCA Model

CA Fries, SD Lawson, LC Wang, CY Villamaria
Vijay Gorantla, MR Davis

Kevin Wu, MD
Research Fellow, US Army Institute of Surgical Research

RESTOR™ Program, 59th Medical Wing, JBSA Lackland AFB

SAGES 2016 Military Surgical Symposium





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



Introduction

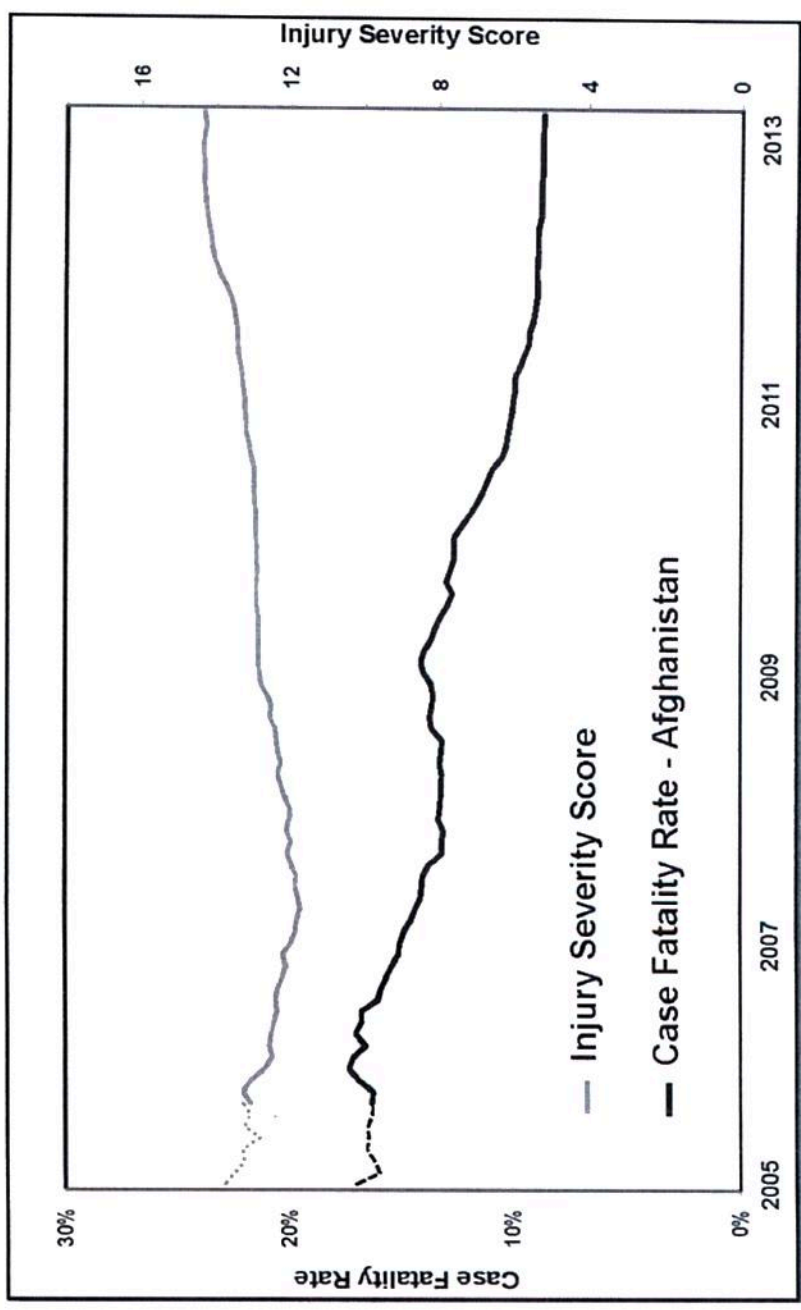


Surviving soldiers from battlefields are presenting with more complex wound patterns in the extremities and face.

The demand for an advanced method of reconstruction, such as Vascularized composite allotransplantation (VCA), is increasing.



Introduction





New rung on the reconstructive ladder

**Vascularized
composite allograft**

Free tissue transfer
eg, latissimus dorsi flap

Regional flaps
eg, posterior interosseous

Local flap
eg, rotational/transposition

Skin graft

Secondary closure

Primary closure



Current limitations to vascularized composite allotransplantation (VCA)

- Requires systemic immunosuppression
- Skin is a primary target for rejection
- Limited donor pool
- Few indications
- Shorter period for ischemia time



Ischemia-reperfusion injury (IRI)

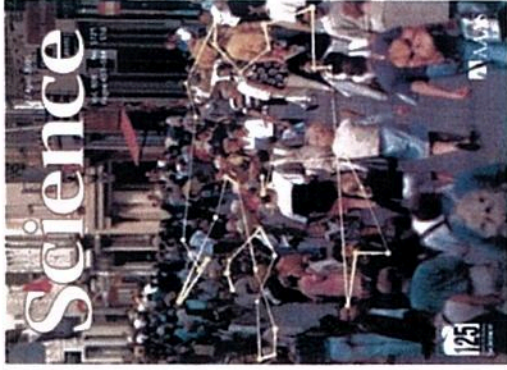
- Exacerbation of cellular/tissue injury after an ischemic insult with re-establishment of blood flow
 - Generation of oxidative stress
 - Microvascular obstruction/thrombosis
 - Neutrophil activation
 - Complement activation
 - Release of anaphylotoxins
- Increasing severity of IRI at time of transplant in solid organs associated with increased rates and severity of acute rejection

Effects of Ischemia and Reperfusion Injury on Long-Term Graft Function

L.R. Requião-Moura, M. de Souza Durão, E.J. Tonato, A.C. Carvalho Matos, K.S. Ozaki, N.O.S. Câmara, and A. Pacheco-Silva



Hydrogen Sulfide



H₂S Induces a Suspended Animation-Like State in Mice

Eric Black Stone, Mike Morrison, Mark B. Roth

Science 22 Apr 2005:

Vol. 308, Issue 5721, pp. 518

DOI: 10.1126/science.1108581

- Reversibly reduce the metabolic rate of mice exposed to 80 ppm of hydrogen sulfide
- Core temperature reduced as much as 11 degrees
- Metabolic rate as judged by carbon dioxide production and oxygen consumption dropped 10-fold
- Animals in this state for 6 hours and they recover completely



Role of H₂S in Large Animals

- Porcine organ transplant model:

BJS

Original Article

Hydrogen sulphide ameliorates ischaemia–reperfusion injury in an experimental model of non-heart-beating donor kidney transplantation†

S. A. Hosgood and M. L. Nicholson*

ISSUO

- In porcine composite flap model:

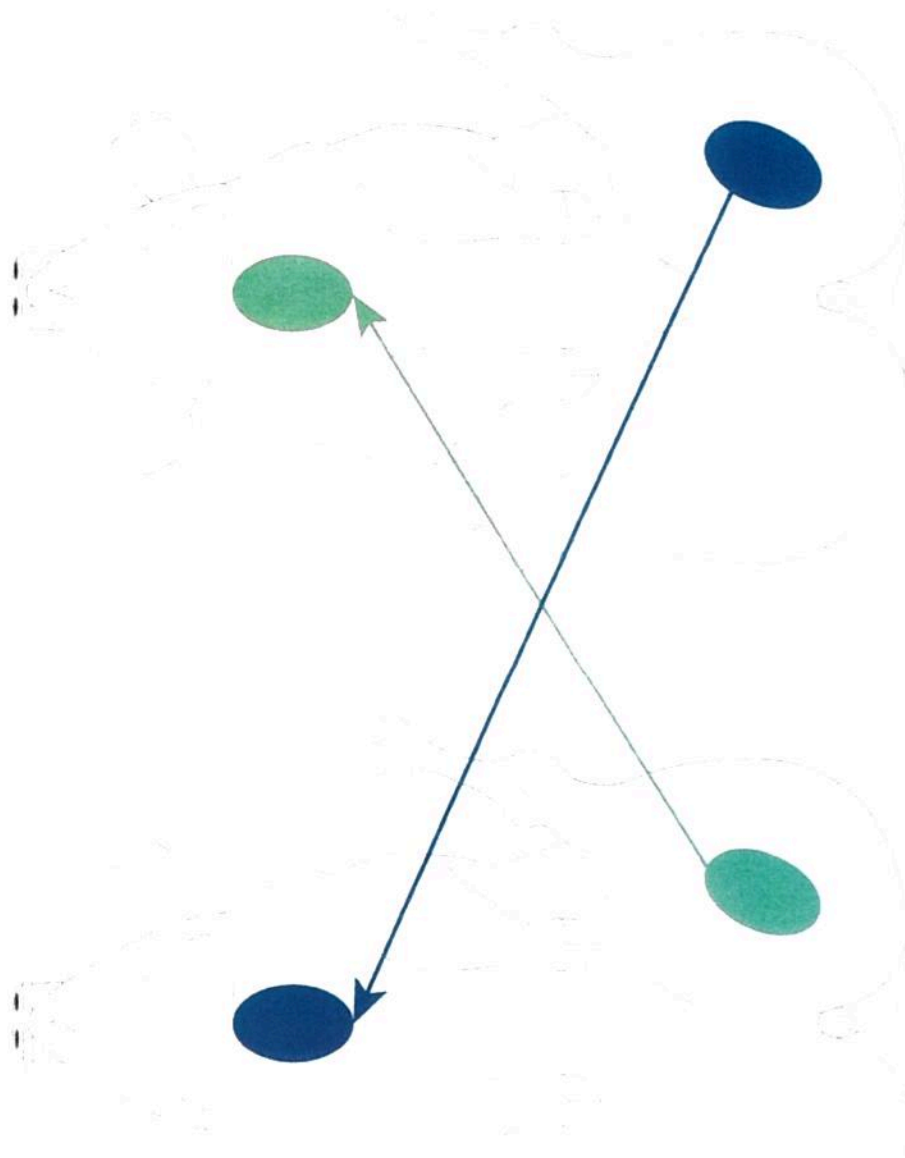
TRANSPLANTATION SURGERY AND RESEARCH

Hydrogen Sulphide Mitigates Reperfusion Injury in a Porcine Model of Vascularized Composite Autotransplantation

Carole Y. Villamaria, MD,*† C. Anton Fries, MA, MRCS,‡ Jerry R. Spencer, BS,†
Mark Roth, MD,§ and Michael R. Davis, MD, FACS†

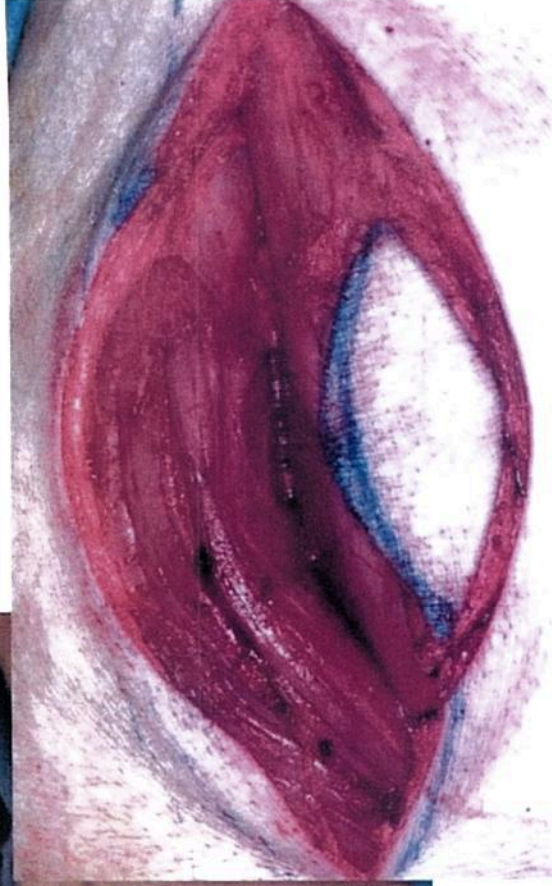
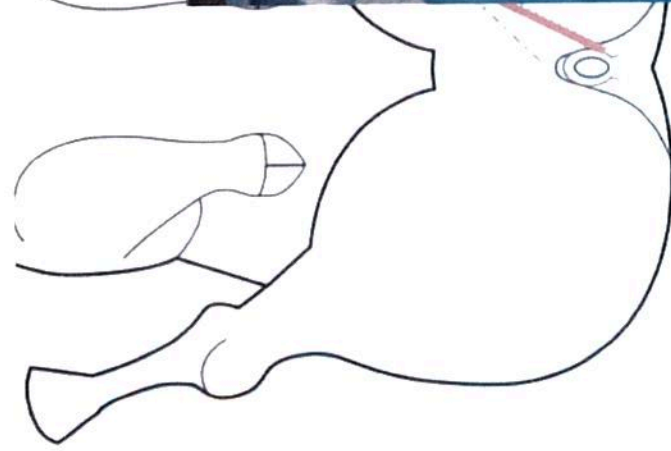


Allotransplantation



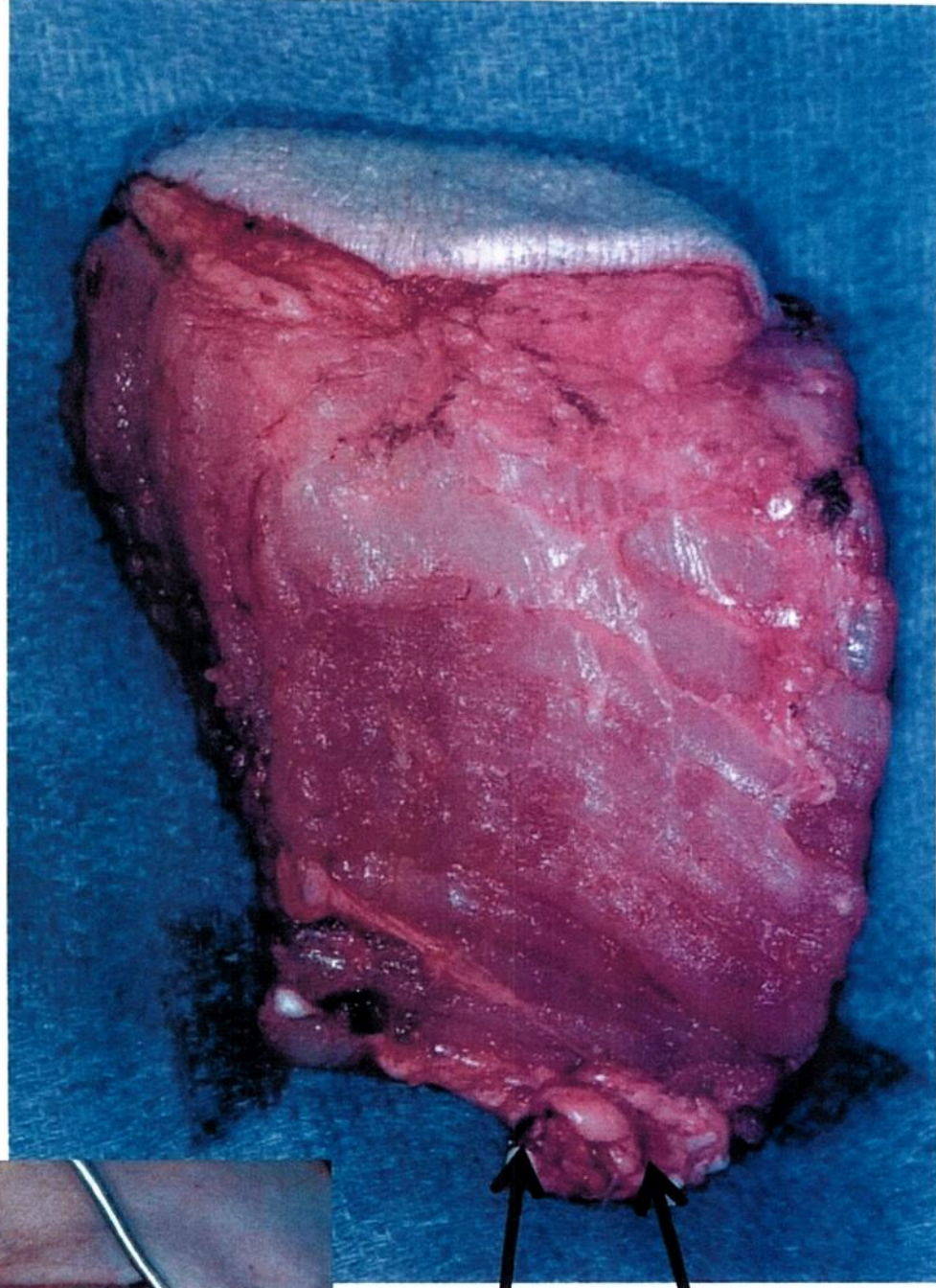
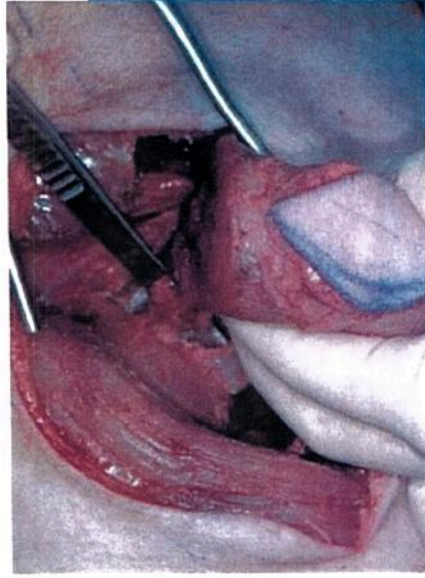


Gracilis myocutaneous VCA model





Gracilis myocutaneous VCA model

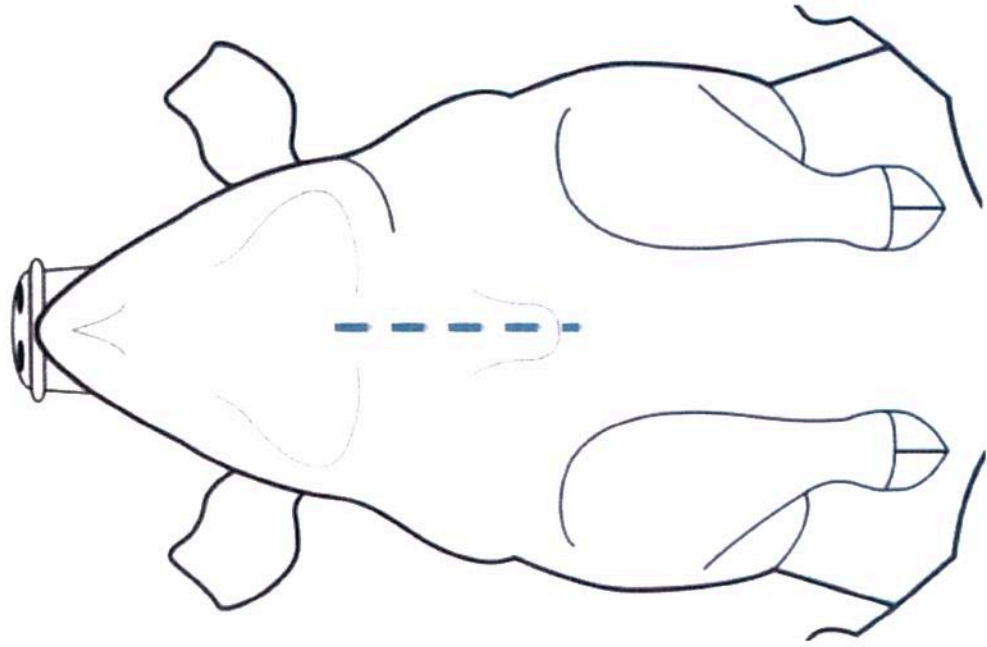


Artery

Vein

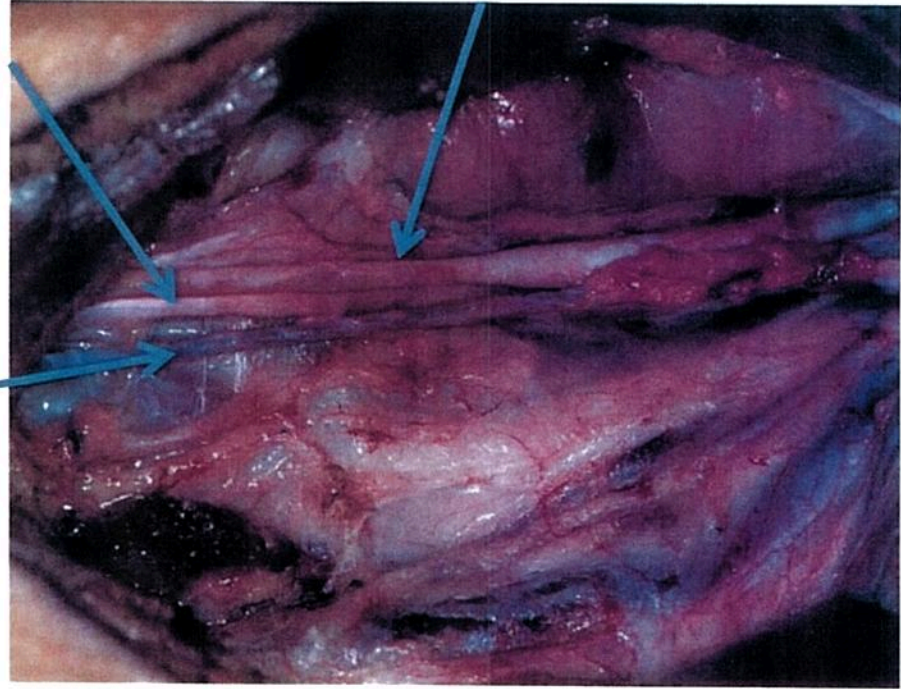


Gracilis myocutaneous VCA model



IJ Vein

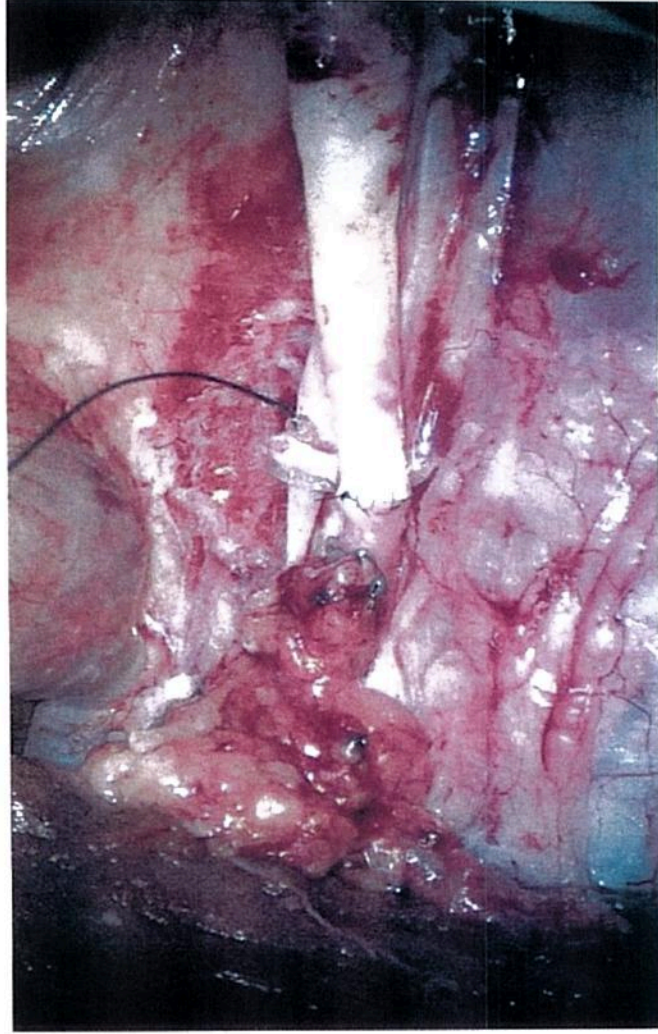
Nerve



External
Carotid
Artery



Gracilis myocutaneous VCA model





Methods

- Single swine leukocyte antigen (SLA) mismatched recipients
- Two groups of 8 animals
 - Group 1 flaps received no additional treatment before transplantation
 - Group 2 flaps received ex-vivo intra-arterial infusion with H₂S solution before transplantation
- Post-operative period
 - 4-mm punch biopsy every 1-3 days for 14 days
 - Blinded histologic examination using Banff working classification



Results



Grade 0



Grade 4



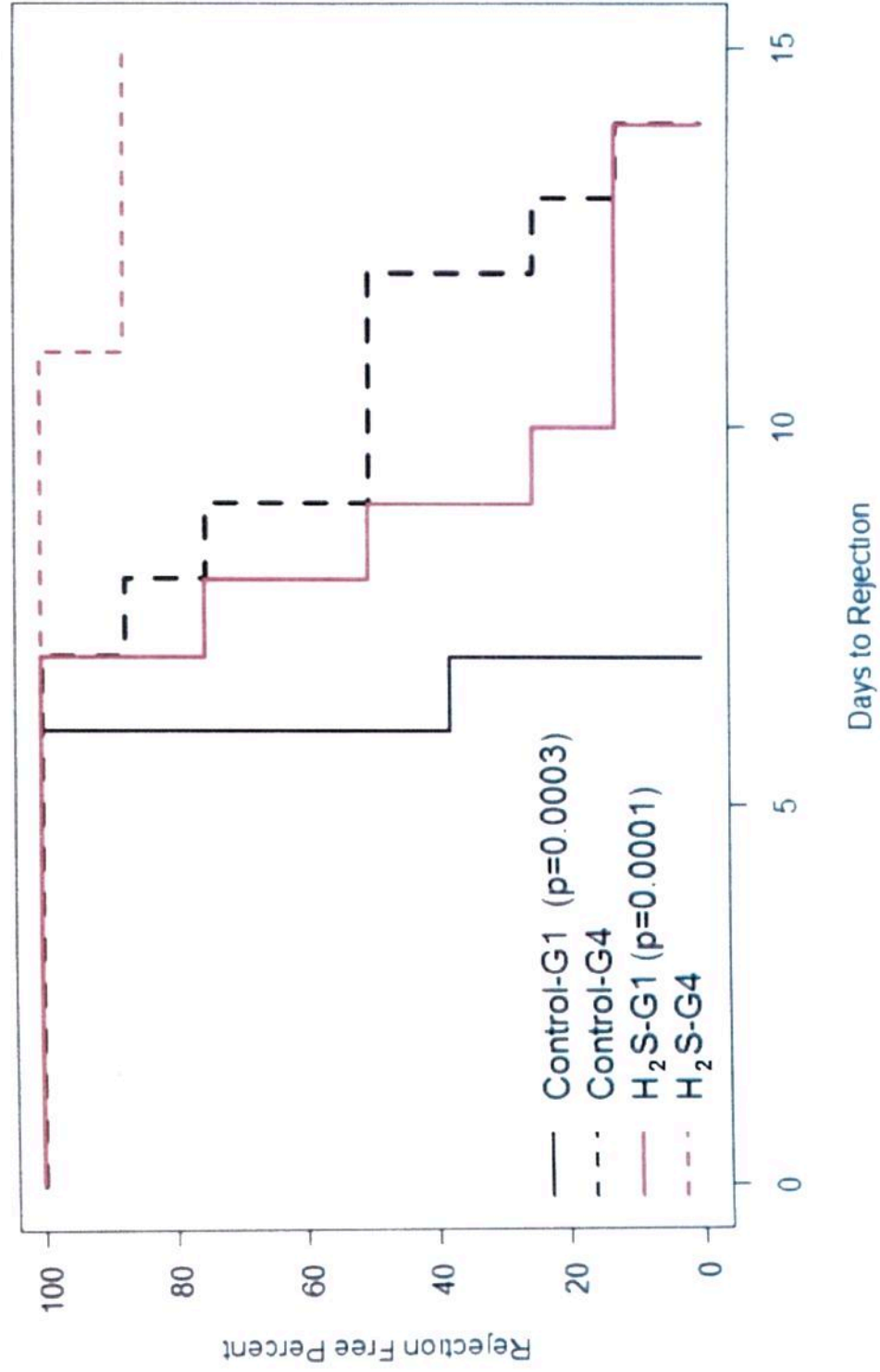
Results

	Grade 1 (time in days to acute rejection)	Grade 4 (time in days to acute rejection)
Controls	Mean: 6.4 SD: 0.52	Mean: 10.5 SD: 2.6
H₂S treated	Mean: 8.9 SD: 2.3 p-value= 0.0095	Mean: >14 days



Results

14 day Rejection by Treatment and Grade





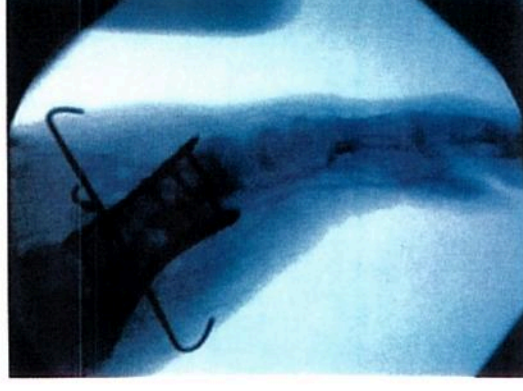
Conclusions

- Swine gracilis myocutaneous flap is a reliable and consistent animal model for studying VCA rejection
- H₂S may play a role in mitigating onset of acute rejection in porcine VCA model in the absence of immunosuppression
- Potential use for graft preservation strategies in a clinical setting that may require prolonged ischemic periods



Future research directions

- Repeat applications of H_2S and H_2Se in limb preservation for Non-human primates (NHP)
- Combination of local immunomodulatory methods, like drug-eluting microparticles or drug-releasing hydrogels
- Application to swine forelimb allotransplantation model





Thank You



References

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