AWARD NUMBER: W81XWH-21-1-0441

TITLE: Nerve Repair with Polyethylene Glycol to Promote Rapid Return of Nerve Function

PRINCIPAL INVESTIGATOR: Dr. Wesley Thayer, MD, PhD

CONTRACTING ORGANIZATION: Vanderbilt University Medical Center (VUMC)
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Nerve Repair with Polyethylene Glycol to Promote Rapid Return of Nerve Function

5a. CONTRACT NUMBER
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5b. GRANT NUMBER
OR200053

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHOR(S)

Dr. Wesley Thayer, MD, PhD
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Vanderbilt University Medical Center (VUMC)
3319 West End Avenue, Ste 970
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

We propose testing the efficacy and safety of a polyethylene glycol (PEG) assisted axonal fusion technique to repair peripheral nerve injuries in humans. After two-year study implementation, we found that our institution continuously worked in a success to deploy this study in our clinical setting, including reliable patient enrollment, implementation of the study protocol into the intraoperative workflow, reliable follow-up of postoperative patients and assessments of drug safety study. So far, we have successfully enrolled 29 patients and completed follow-ups for 11 patients. Preliminary data has been summarized in one manuscript for peer-review.

15. SUBJECT TERMS
PEG; Polyethylene glycol; Nerve; Transection; Injury

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
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1. INTRODUCTION

Current strategies for peripheral nerve repair are severely limited. Recently the axonal fusion technique by using a hydrophilic-compound polyethylene glycol (PEG) emerges as a promising approach to promote early repair with functional recovery after peripheral nerve injuries. Preclinical data based on the published reports and our own *in vivo* studies have demonstrated that PEG based repair can restore compound action potential (CAP) immediately and improve functional recovery significantly after a peripheral nerve injury, which suggest that we can offer a novel therapy to test in humans who have experienced such injuries. We propose testing the efficacy and safety of a polyethylene glycol (PEG) assisted axonal fusion technique to repair peripheral nerve injuries in humans. We hypothesize that PEG fusion of human sensory nerve injuries at the site of epineural repair will result in improved return of physiologic function as compared to controls without PEG. Also, for mixed nerves containing both motor and sensory axons with segmental defects up to 3 cm, PEG delivery at both autograft repair coaptation sites will restore early safe function. These repairs must be performed within 72h after injury before Wallerian degeneration prevents rescue of the distal axons. We also hypothesize that PEG safety profile will be within acceptable limits for early clinical implementation and allow for expansion to multicenter trials.

2. KEYWORDS

PEG; Polyethylene glycol; Nerve; Transection; Injury

3. ACCOMPLISHMENTS

- **What were the major goals of the project?**

Specific Aim 1: Determine if coaptation site delivery of PEG is superior to repair alone for lacerated nerves requiring simple epineural repair in human upper extremity sensory nerve injuries.

Specific Aim 2: Determine if dual coaptation site delivery of PEG with autografts is superior to autograft alone for segmental defects in human upper extremity injuries.

- **What was accomplished under these goals?**

Specific Aim 1: Determine if coaptation site delivery of PEG is superior to repair alone for lacerated nerves requiring simple epineural repair in human upper extremity sensory nerve injuries.	**Timeline**	**Completed/ In Progress/ Not Initiated**
	Months	
Major Task 1: Approvals from regulatory agencies		
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study		
Review IRB documents and confirm approval status	1-24	Completed
Submit any changes to VUMC Central IRB review	1-24	Completed
Submit for USAMRDC review (ORP/HRPO)	1-24	Completed
Review IND documents and confirm approval status	1-24	Completed
Clinicaltrial.gov registration	1-24	Completed
Submit amendments, adverse events and protocol deviations as needed	As Needed	Completed and continues to occur
Coordinate with IRB for annual continuing review	Annually	Completed and continues to occur
Milestone Achieved: Local IRB approval through VUMC	1-24	Completed and continues to occur
Milestone Achieved: HRPO approval for all protocols	1-24	Completed and

		continues to occur
Major Task 2: Coordinate Study Staff for Clinical Trials		
Subtask1: Hiring and Training of Study Staff		
Advertise and interview for TBD project related staff	1-24	Completed
Coordinate hiring and training TBD staff	1-24	Completed
Milestone Achieved: Research staff trained	1-24	Completed
Major Task 3: Participant Recruitment, Intervention, Follow-up/Participant Evaluation		
Subtask 1: Recruitment		
Coordinate with team members for all study steps, evaluations, data collection and database requirements	1-24	Completed
Finalize assessment measurements	1-24	Completed
Milestone Achieved: 1st participant consented, screened and enrolled	1-24	Completed
Milestone Achieved: Study begins	1-24	Completed
Subject recruitment	1-24	In Progress
Participants evaluated pre and post-surgical repair. N=60 randomly assigned to Group 1 (treatment) or Group 2 (control)	1-24	In Progress
Milestone Achieved: 100 patients screened	1-24	In Progress
Subtask 2: Follow-up and Interim Safety Analysis		
Complete follow-up assessments 12 months post-surgical intervention	1-24	In Progress
Perform safety analysis every 10 patients enrolled	As needed	Completed and continues to occur
Milestone Achieved: Statistical Analysis shows no adverse response to treatment.	As Available, every 10 pts	Completed and continues to occur
Major Task 4: Data Analysis		
Subtask 1: Coordinate with study personnel to finalize data collection and data quality		
Perform all analyses according to specifications, share output and finding with all investigators	25-30	Future
Dissemination of findings (abstracts, presentation, publications, DOD)	25-36	Future
Milestone Achieved: Report results from data analyses	25-36	Future
Subtask 2: Data Analysis		
Final data analysis	25-36	Future
Milestone Achieved: Report	25-36	Future

Specific Aim 2: Determine if dual coaptation site delivery of PEG with autografts is superior to autograft alone for segmental defects in human upper extremity injuries.	**Timeline**	**Completed/ In Progress/ Not Initiated**
	Months	
Major Task 1: Approvals from regulatory agencies.		
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study		
Review IRB documents and confirm approval status	1-24	Completed
Submit any changes to VUMC Central IRB review	1-24	Completed
Submit for USAMRDC review (ORP/HRPO)	1-24	Completed
Review IND documents and confirm approval status	1-24	Completed
Clinicaltrial.gov registration	1-24	Completed
Submit amendments, adverse events and protocol deviations as needed	As Needed	Completed and continues to occur

Coordinate with IRB for annual continuing review	1-24	Completed and continues to occur
Milestone Achieved: Local IRB approval through VUMC	1-24	Completed and continues to occur
Milestone Achieved: HRPO approval for all protocols	1-24	Completed and continues to occur
Major Task 2: Coordinate Study Staff for Clinical Trials		
Subtask1: Hiring and Training of Study Staff		
Advertise and interview for TBD project related staff	1-24	Completed
Coordinate hiring and training TBD staff	1-24	Completed
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Major Task 3: Participant Recruitment, Intervention, Follow-up/Participant Evaluation		
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Finalize assessment measurements	1-24	Completed
Milestone Achieved: 1st participant consented, screened and enrolled	1-24	Completed
Milestone Achieved: Study begins	1-24	Completed
Subject recruitment	1-24	In Progress
Participants evaluated pre and post surgical repair. N=60 randomly assigned to Group 1 (treatment) or Group 2 (control)	1-24	In Progress
Milestone Achieved: 100 patients screened	1-24	In Progress
Subtask 2: Follow-up and Interim Safety Analysis		
Complete follow-up assessments 12 months post-surgical intervention	25-42	Future
Perform safety analysis every 10 patients enrolled	As needed	Completed and continues to occur
Milestone Achieved: Statistical Analysis shows no adverse response to treatment.	As available, every 10 pts	Completed and continues to occur
Major Task 4: Data Analysis		
Subtask 1: Coordinate with study personnel to finalize data collection and data quality		
Perform all analyses according to specifications, share output and finding with all investigators	25-42	Future
Dissemination of findings (abstracts, presentation, publications, DOD)	25-48	Future
Milestone Achieved: Report results from data analyses	25-48	Future
Subtask 2: Data Analysis		Future
Final data analysis	25-48	Future
Milestone Achieved: Report	25-48	Future

Human Use Regulatory Protocols
TOTAL PROTOCOLS: 1

PROTOCOL (1 of 1 total):
Protocol [HRPO Assigned Number]: E02442.1a
Title: Nerve Repair Using Hydrophilic Polymers to Promote Immediate Fusion of Severed Axons and Swift Return of Function
Target required for clinical significance: 120 subjects
Target approved for clinical significance: 120 subjects

Status:

(i) Number of subjects recruited/original planned target: 135/120
Number of subjects screened/original planned target: 135/120
Number of patients consented/original planned target: 49/120
Number of patients enrolled/original planned target: 29/120
Number of patients completed/original planned target: 11/120

Of the patients consented, there were 20 patients who had to be withdrawn by the study team due to lacking neve injury or failing the inclusion criteria.

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: An amendment submitted to increase patient compensation to cover the patient's travelling cost for follow-up visits has been approved by VUMC IRB and USAMRMC HRPO on OCT 2022.

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

- None

- **What opportunities for training and professional development has the project provided?**

  This grant helped advance the training directly of three research fellows who are now involved with plastic surgery clinical research and provided research opportunities for the career development of junior faculty Dr. Manzanera.

- **How were the results disseminated to communities of interest?**

  Nothing to Report

- **What do you plan to do during the next reporting period to accomplish the goals?**

  We will continue to screen and recruit subjects and complete follow-ups for enrolled subjects.

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing to Report

- **What was the impact on other disciplines?**

  Nothing to Report

- **What was the impact on technology transfer?**

  Nothing to Report

- **What was the impact on society beyond science and technology?**

  Nothing to Report

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**

  Nothing to Reports

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Nothing to Report

- **Changes that had a significant impact on expenditures**

  Nothing to Report

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

  Nothing to Report

- **Significant changes in use or care of human subjects**
  Nothing to Report

- **Significant changes in use or care of vertebrate animals**
  Nothing to Report

- **Significant changes in use of biohazards and/or select agents**
  Nothing to Report

6. PRODUCTS

- **Publications, conference papers, and presentations**

1. Sriya Nemani. Podium Presentation at the Southeastern Society for Plastic and Reconstructive Surgeons 66th Annual Meeting, *June 2023.*

2. Nemani S, Chaker S,Ismail H, Yao J, Chang M, Kang H,Desai M, Weikert D, Bhandari PL,Drolet B, Sandvall B, Hill JB and Thayer W. Polyethylene Glycol-mediated Axonal Fusion Promotes Early Sensory Recovery After Digital nerve Injury. *Submitted, June 2023.*

- **Website(s) or other Internet site(s)**

  Nothing to Report

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**

  Nothing to Report

7. PARTICIPANTS &OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Wesley Thayer
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-6512-6312
Nearest person month worked:	1.2
Contribution to Project:	Dr. Thayer has assisted with ensuring study is launched according to protocol, as well as performing some of the operative procedures of the enrolled patients.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Isaac Manzanera Esteve
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-9282-7026
Nearest person month worked:	2.0
Contribution to Project:	Dr. Manzanera has assisted with ensuring the study was launched according to protocol.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Julia Yao
Project Role:	Research Nurse Practitioner
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	5.5
Contribution to Project:	Ms Yao has assisted with subject enrollment and ensuring the study was launched according to protocol.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Helen Ismail
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	7.1
Contribution to Project:	Ms Ismail has assisted with subject enrollment and postoperative clinical testing of nerve repair outcomes.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Sara Chaker
Project Role:	Clinical Research Fellow
Researcher Identifier (e.g. ORCID ID):	0000-0002-5259-0941
Nearest person month worked:	2.0
Contribution to Project:	Ms Chaker has assisted with subject enrollment, operating room protocol guidance, and postoperative clinical testing of nerve repair outcomes.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Sriya Nemani
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	2.0
Contribution to Project:	Ms Nemani has assisted with subject enrollment, operating room protocol guidance, and postoperative clinical testing of nerve repair outcomes.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Ling Yan
Project Role:	Staff Scientist
Researcher Identifier (e.g. ORCID ID):	0000-0001-5727-3278
Nearest person month worked:	0.8
Contribution to Project:	Dr. Yan has assisted with ensuring study materials are adequately stocked and that participating team members are appropriately credentialled.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Ya-Ching Hung
Project Role:	Clinical Research Fellow
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	0.6
Contribution to Project:	Dr. Hung has assisted with subject enrollment, operating room protocol guidance, and postoperative clinical testing of nerve repair outcomes.
Funding Support:	Vanderbilt Department of Plastic Surgery and this grant

Name:	Hakmook Kang
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0.6
Contribution to Project:	Dr. Kang provides statistical support for the project.
Funding Support:	

- **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

- **What other organizations were involved as partners?**

  Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**

  Nothing to Report

- **QUAD CHARTS:**

  Attachment by Dr. Thayer

9. APPENDICES

Financial Report

Thayer: OR200053
W81XWH-21-1-0441/Nerve Repair with Polyethylene Glycol to Promote Rapid Return of Nerve Function

Year 1 07/01/21-06/30/22

	Budget	Actual	Balance
Personnel	$ 198,750.84	$ 207,209.09	$ (8,458.25)
Supplies	$ 11,897.56	$ 5,342.49	$ 6,555.07
Travel	$ 2,651.27	$ 269.85	$ 2,381.42
Subcontract		$ -	$ -
Indirects	$ 155,708.75	$ 155,358.76	$ 349.99
Total	$ 369,008.42	$ 368,180.19	$ 828.23

Year 2 07/01/22-06/30/23 **To date through June 2023**

	Budget	Actual	Balance
Personnel	$ 202,725.88	$ 213,066.25	$ (10,340.37)
Supplies	$ 11,834.28	$ 3,070.11	$ 8,764.17
Travel	$ 2,651.27	$ -	$ 2,651.27
Subcontract		$ -	$ -
Indirects	$ 158,564.34	$ 160,181.15	$ (1,616.81)
Total	$ 375,775.77	$ 376,317.51	$ (541.74)

Year 3 07/01/23-06/30/24

	Budget	Actual	Balance
Personnel	$ 206,780.37		$ 206,780.37
Supplies	$ 7,571.00		$ 7,571.00
Travel	$ 2,651.27		$ 2,651.27
Subcontract			$ -
Indirects	$ 158,411.91		$ 158,411.91
Total	$ 375,414.55	$ -	$ 375,414.55

Year 4 07/01/24-06/30/25

	Budget	Actual	Balance
Personnel	$ 210,915.99		$ 210,915.99
Supplies	$ 5,971.00		$ 5,971.00
Travel	$ 2,651.30		$ 2,651.30
Subcontract			$ -
Indirects	$ 160,262.97		$ 160,262.97
Total	$ 379,801.26	$ -	$ 379,801.26

Grant Project to Date Actual	**Through December 2022**		
	Budget	Actual	Balance
Personnel	$ 819,173.08	$ 420,275.34	$ 398,897.74
Supplies	$ 37,273.84	$ 8,412.60	$ 28,861.24
Travel	$ 10,605.11	$ 269.85	$ 10,335.26
Subcontract	$ -		$ -
Indirects	$ 632,947.97	$ 315,539.91	$ 249,713.72
Total	$ 1,500,000.00	$ 744,497.70	$ 687,807.96

Budget Award Year	
1	$ 369,008.42
Year 2	$ 375,775.77
Year 3	$ 375,414.55
Year 4	$ 379,801.26
	$ 1,500,000.00

Nerve Repair with Polyethylene Glycol to Promote Rapid Return of Nerve Function.

OR200053 W81XWH-20-PRORP-CTRA

PI: Wesley Thayer MD/PhD, Hakmook Kang PhD, Isaac Esteve PhD:

Org: Vanderbilt University Medical Center **Award Amount: $1,500,00.00**

Study/Product Aim(s)

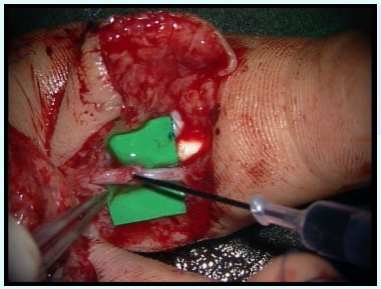
•PEG fusion of human nerve injuries will result in near immediate return of physiologic function compared to controls for both simple nerve repairs and for repairs nerves with segmental defects using autografts.

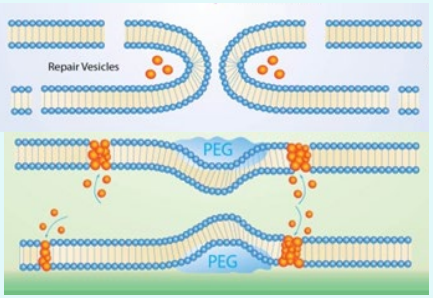
Aims:

1 Determine if coaptation site delivery of PEG with is superior to repair alone

2 Determine if dual coaptation site delivery of PEG with autografts is superior to autograft alone: segmental mixed nerve defects

Approach: This randomized, prospective clinical trial will \ evaluate the axonal fusion using two distinct cohorts of upper extremity nerve injury patients. Patients will either receive standardized neurorrhaphy which relies on predictably slow axonal outgrowth, or + PEG, which promotes axonal fusion allowing for rapid nerve recovery. 2 groups will be studied: simple repair, and repair w up to 3 cm autografts.





- Left -Human digital nerve undergoing PEG fusion repair
- Right- PEG fuses approximated axons back together after suture repair.

Accomplishment: IRB approval, research team recruited and trained, 269patients enrolled.

Timeline and Cost

Activities CY	21	22	23	24	25
Aim 1 recruitment					
Aim 2 recruitment					
Follow up (both aims)					
Data analysis					
Estimated Budget ($K)	**$93.8**	**$375**	**$375**	**$375**	**$281**

Updated: (7/27/2023)

Goals/Milestones

CY21Goal – Recruit patients

X Vanderbilt IRB approval obtained

X Research team recruited and trained; 28 consented, 19 enrolled

CY22 Goals – Continue clinical trial

X Underway - small (digital) , manuscript submitted

X Underway large (mixed) nerve recruitment

CY23 Goal –

X Continue nerve recruitment

CY24 Goal – Follow Up

☐ Complete small (digital) and large (mixed) nerve follow up

CY25 Goal –Complete large (mixed) nerve testing

☐ Complete large (mixed) nerve testing

☐ Data analysis and publication

Comments/Challenges/Issues/Concerns: none

Budget Expenditure (from last quarter- new #'s pending)

Projected $745K/Actual Expenditure:$ 744: Cost normalizing as more pts enrolled.