

Award Number: W81XWH-12-2-0128

TITLE: Instructive Biologic Scaffold for Functional Tissue Regeneration Following Trauma to the Extremities

PRINCIPAL INVESTIGATOR: CAPT Mark Fleming, CAPT, MC, USN

CONTRACTING ORGANIZATION: The Geneva Foundation
Tacoma, WA 98402

REPORT DATE: September 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE September 2015		2. REPORT TYPE Annual		3. DATES COVERED 30 Sep 2014 - 29 Aug 2015	
4. TITLE AND SUBTITLE Instructive Biologic Scaffold for Functional Tissue Regeneration Following Trauma to the Extremities				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-12-2-0128	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Mark E. Fleming, Leon Nesti E-Mail: mark.e.fleming.mil@mail.mil , leon.j.nesti.mil@mail.mil				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Geneva Foundation 917 Pacific Ave, Suite 600 Tacoma, WA 98402				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release, Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Our hypothesis is that subjects who receive the SIS-ECM scaffold material will have significant new muscle growth and improvements in strength in the treated extremity. The proposed prospective, non-randomized, two-armed study in forty (40) subjects will establish the safety and effectiveness of a regenerative scaffold for the restoration of functional musculotendinous tissue, including the restoration of blood supply and innervation. Cohort 1 will include 20 subjects with upper extremity flexor and extensor traumatic, postoperative, or other avulsive VML. Cohort 2 will include 20 subjects with open femur fractures or soft tissue injury to the thigh resulting in VML. The primary endpoint will be changes in graft site muscle volume compared to baseline at 6 and 12 months as determined by imaging.					
15. SUBJECT TERMS Regenerative Medicine; Extracellular Matrix; Volumetric Muscle Loss					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRAA
			UU	34	19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION: The purpose of this investigation is to evaluate the effectiveness of a regenerative biologic scaffold, Biodesign® 6-layer Plastic Surgery Matrix [Cook Biotech]; Premarket Notification Trade/Device Name: SIS Plastic Surgery Matrix, derived from small intestinal submucosa extracellular matrix (SIS-ECM), for the restoration of functional musculotendinous tissue in participants with an acute or subacute volumetric muscle loss (VML) injury. The proposed research is a prospective, multi-center, non-randomized, single-armed, two-cohort clinical trial with a targeted population of forty (40) evaluable subjects. Cohort 1 will include 20 subjects with upper extremity traumatic, postoperative, or other avulsive VML injury. Cohort 2 will include 20 subjects with lower extremity traumatic, postoperative, or other avulsive VML injury. This study will be conducted at 2 study sites: Walter Reed National Military Medical Center (WRNMMC) and the R Adams Cowley Shock Trauma Center (STC) at the University of Maryland Medical Center. Study participants will be enrolled and followed for a period of 1 year (12 months). This study will evaluate the effectiveness of Biodesign®, a 6-layer regenerative biologic scaffold derived from small intestinal submucosa extracellular matrix (SIS-ECM), for the restoration of functional musculotendinous tissue in forty (40) participants, both male and female, with an acute or subacute volumetric muscle loss (VML) defects in their upper or lower extremities. The targeted subject population will consist of injured service members or civilian victims of trauma. All subjects enrolled will receive the SIS-ECM scaffold, trimmed to fit the defect, and will serve as their own control. Only one segmental muscle defect will be treated in each subject, and each subject may receive multiple SIS-ECM grafts at the injury site. Enrolled participants will be assigned to 1 of 2 Cohort groups. Cohort 1 will include 20 subjects with upper extremity traumatic, postoperative, or other avulsive VML injury. Cohort 2 will include 20 subjects with lower extremity traumatic, postoperative, or other avulsive VML injury.

2. KEYWORDS: Regenerative Medicine; Extracellular Matrix; Volumetric Muscle Loss

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Our hypothesis is that subjects who receive the SIS-ECM scaffold material will have significant new muscle growth and improvements in strength in the treated extremity. The proposed prospective, non-randomized, two-armed study in forty (40) subjects will establish the safety and effectiveness of a regenerative scaffold for the restoration of functional musculotendinous tissue, including the restoration of blood supply and innervation. Cohort 1 will include 20 subjects with upper extremity flexor and extensor traumatic, postoperative, or other avulsive VML. Cohort 2 will include 20 subjects with open femur fractures or soft tissue injury to the thigh resulting in VML. The primary endpoint will be changes in graft site muscle volume compared to baseline at 6 and 12 months as determined by imaging. Secondary endpoints will include histopathological characterization of the muscle healing response at the graft site, clinician and subject evaluation of cosmesis, and comparison of complication rates to clinical site historical standard of care.

What was accomplished under these goals?

Specific Aim 1: To induce the *de novo* formation of at least 25% of the missing muscle tissue using an inductive ECM scaffold. This tissue will be morphologically and structurally identical to native skeletal muscle tissue.

Briefly, Cook BioDesign's Plastic Surgery Matrix® device will be implanted surgically. Change in muscle volume from baseline at device implantation as determined by MRI or CT will be assessed. Biopsied tissue will be fixed and the tissue specimens will be subjected to a battery of immunohistochemical, immunolabeling, and traditional histochemical stains for the identification of cell phenotype, extracellular matrix characterization, and histomorphometric analysis. The main endpoint of this study is to determine the percentage of volume restored at the surgical site.

Task 1: IRB and Facility Approvals (months 1-4)

1a. IRB Approval (months 1-4)

Facility: Walter Reed National Military Medical Center (WRNMMC)

1b. IRB Approval (months 1-4)

Facility: Maryland Shock Trauma (MST)

1c. Approval by USAMRMC Office of Research Protections (months 4-5)

The overall study protocol is being developed and written by WRNMMC as the coordinating center and will then be sent to the MST for inclusion into their site specific protocol. MST cannot submit the protocol to the IRB, until the WRNMMC master protocol has been approved by WRNMMC's IRB Oversight Committee and DoD HRPO. The protocols are drafted and being finalized with investigators and collaborators for submission. As required prior to IRB submission, the WRNMMC protocol was submitted to the departmental Scientific Review Committee (SRC) for review and received back with minimal questions and edits. The WRNMMC protocol and CRFs are being finalized for IRB administrative and committee review. Kick-off meetings via conference call were conducted on 16 September 2014 with WRNMMC personnel and on 30 October 2014, including current PI, Mr. Janis, and transitioning PI, CDR Fleming, to discuss study roles and responsibilities. Another meeting was conducted on 13 November 2014 between WRNMMC study personnel with the addition of WRNMMC personnel Dr. Dearth and Ms. Pruziner to clarify roles. Additional meetings were conducted on 04 February 2015, 19 February 2015, 12 March 2015, 2 April 2015, 04 June 2015, 11 June 2015, 23 June 2015, 29 October 2015 with WRNMMC study personnel to discuss and clarify study protocol specifics and progress. Conference call meetings were conducted on 04 March 2015, 02 September 2015, 16 September 2015, 30 September 2015 between WRNMMC and MST, including WRNMMC PI CDR Fleming and MST PI Dr. Sciadini, to discuss study protocol and site coordination specifics. An in-person investigators' meeting between WRNMMC and MST was conducted on 27 August 2015, including WRNMMC transitioning PI, LTC Nesti, MST PI Dr. Sciadini, WRNMMC investigator Dr. Dearth, and WRNMMC and MST study coordinators, Ms. Lee and Ms. Ordonio to discuss changes in study personnel and progress. Another in-person investigators' meeting between WRNMMC and MST was conducted on 23 September 2015 at MST with Dr. Dearth and Ms. Pruziner presenting and discussing study protocol with MST investigators. A conference call meeting was conducted on 05 August 2015 with the addition of STATKING personnel to clarify roles and responsibilities. In-person meetings to discuss CRFs were conducted on 04 September 2015 with WRNMMC & MST study personnel and on 21 September 2015 with WRNMMC study personnel.

Task 2: Patient Enrollment (months 5-23)

2a. Patient Enrollment (months 5-23)

Facility: Walter Reed National Military Medical Center

2b. Patient Enrollment (months 5-23)

Facility: Maryland Shock Trauma

Clinical Patients: 40

Patient Enrollment has not yet begun.

Task 3: Patient Follow Up (months 8-31)

3a. CT Guided Biopsy (months 8-31)

Facility: Walter Reed National Military Medical Center

3b. MRI, MRI Guided Biopsy (months 8-31)

Facility: Maryland Shock Trauma

Clinical Patients: 40

Patient Follow Up has not yet begun.

Task 4: Histology/Pathology (months 8-35)

4a. Histology (months 8-35)

Facility: WRNMMC

4b. Pathology (months 8-35)

Tissue Samples: 80

Histology and Pathology has not yet begun.

Task 5: Final Report (months 35-37)

5a. Review of Data and Generation of Final Report (months 35-37)

Facility: WRNMMC

Pathology reports, functional test scores, and imaging data will be assessed by Dr. Leon Nesti and study personnel. These data will be tabulated and forwarded to the biostatistician for statistical analysis as described in the statistical plan. A final report incorporating these data will be prepared, reviewed and accepted by the PIs at WRNMMC and Maryland Shock Trauma.

Review of Data and Final Report has not yet begun.

Specific Aim 2: To restore at least 25% of the function of the involved muscle group through the use of an inductive ECM scaffold material.

Briefly, functional recovery in the injured extremity will be compared at 1, 4, 8, and 12 months. At 12 months, function of the injured extremity will be compared to the contralateral limb, if present. The main endpoint of this study is to determine the percentage of function restored to the surgical site.

Task 6: Patient Follow Up (months 8-31)

6a. Functional and Physician Assessment (months 8-31)

Facility: Walter Reed National Military Medical Center

6b. Functional and Physician Assessment (months 8-31)

Facility: Maryland Shock Trauma

Clinical Patients: 40

Patient Follow Up has not yet begun.

Task 7: Final Report (months 31-47)

7a. Review of Data and Generation of Final Report (months 31-47)

Facility: WRNMMC

Pathology reports, functional test scores, and imaging data will be assessed by the research team at WRNMMC. These data will be tabulated and forwarded to the biostatistician for statistical analysis as described in the statistical plan. A final report incorporating these data will be prepared, reviewed, and accepted by investigators.

Review of Data and Final Report has not yet begun.

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

Training and professional development activities occurred between current and former investigators and collaborators at the Military Health System Research Symposium (MHSRS), Ft Lauderdale, Florida in August 2015 and also at the Tissue Engineering and Regenerative Medicine International Society (TERMIS) World Conference, Boston, Massachusetts in September 2015.

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?

The WRNMMC protocol will be submitted for WRNMMC IRB administrative and committee review. After the WRNMMC master protocol has been approved by WRNMMC's IRB Oversight Committee and DoD HRPO, it will be sent to the MST for inclusion into their site specific protocol and MST IRB submission.

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

Functional recovery in the injured extremity will be compared at 1, 4, 8, and 12 months as opposed to 3, 6, 9 months as originally stated in the SOW. Based on previous studies, earlier remodeling time points are of greater scientific interest.

Primary endpoint will be to restore at least 25% of the function of the involved muscle group. Secondary endpoints will include to induce the *de novo* formation of at least 25% of the missing muscle tissue using an inductive SIS-ECM scaffold, as determined by quantitative image analysis,

compared to baseline at 8 and 12 months.

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

We are anticipating delays in the establishment of a CRADA due to transitioning of personnel in the CRADA office as well as transitions between current approved template standards and new DHA standards. We are working to mitigate this issue by having continuous, ongoing conversations with WR staff to ensure we are on the correct path forward and no efforts have been lost. We also anticipate changes in histology assessment due to budgetary constraints and will identify an alternate route within such budgetary constraints. Additionally, we are working to mitigate the issue of outstanding MIPR'd funds to WRNMMC for study purposes and investigating the avenues and options to resolve the matter. We are doing this by initiating conversations with DRP, Resource Management Officers on site and CDMRP to help resolve the issue. To date, we have not been able to confirm the ability to receive and route funds appropriately, but hope to have resolution to this issue in the coming months.

Changes that had a significant impact on expenditures

Due to the delay in IRB submission, anticipated costs have been significantly lower than expected. We have delayed hiring staff. Our sub recipient has also delayed their timeline and costs while we work to finalize the Coordinating Center protocol. Once these milestones have been met, we anticipate an increase in costs as the program moves forward.

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

Nothing to Report

6. PRODUCTS:

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	CAPT Mark Fleming, CAPT, MC, USN
Project Role:	Principal Investigator (PI) / Site Principal Investigator at WRNMMC
Nearest person month worked:	12 months
Contribution to Project:	Dr. Fleming is an orthopedic trauma surgeon, was the site Principal Investigator (PI) at WRNMMC and then transitioned to take over the role of study PI from Abram Janis.
Name:	LTC Leon Nesti, MD, PhD
Project Role:	LTC, MC, USA Principal Investigator (PI) / Site Principal Investigator at WRNMMC

Nearest person month worked:	Associate Professor, Uniformed Services University 2 months
Contribution to Project:	Dr. Nesti is a hand and upper extremity orthopedic reconstructive surgeon at WRNMMC who has transitioned to take over the role of study PI from Dr. Fleming, and has extensive research experience.
Name:	Marcus Sciadini, MD
Project Role:	Site Principal Investigator at MST
Nearest person month worked:	12 months
Contribution to Project:	Dr. Sciadini is an orthopedic trauma surgeon and the site Principal Investigator (PI) at MST, provided clinical expertise and input on study protocol and design.
Name:	Barry Martin, COL, MC, USA
Project Role:	Associate Investigator, Plastic & Reconstructive Surgeon
Nearest person month worked:	9 months
Contribution to Project:	Dr. Martin, is a reconstructive plastic surgeon, has provided expertise in soft tissue reconstruction, clinical applications of regenerative medicine, and provided input on study protocol and design.
Name:	Ian Valerio, MD, MS, MBA, FACS CDR, MC, USNR
Project Role:	Collaborator / Consultant
Nearest person month worked:	6 months
Contribution to Project:	Dr. Valerio, is a reconstructive plastic surgeon, former Co-Investigator (Co-I) at WRNMMC, and has provided expertise in soft tissue reconstruction, clinical applications of regenerative medicine, and provided input on study protocol and design.
Name:	Christopher Dearth, PhD
Project Role:	Associate Investigator & Subject Matter Expert at WRNMMC
	Facility Research Director, DoD-VA Extremity Trauma & Amputation Center of Excellence
Nearest person month worked:	11 months
Contribution to Project:	Dr. Dearth is a Scientist Subject Matter Expert at WRNMMC, facility research director, has expertise in muscle regenerative research, provided input on study protocol and design, and will assist with processing biopsies, histological evaluations and publications.
Name:	Alison Pruziner, PT, DPT, ATC
Project Role:	Associate Investigator & Research Physical Therapist at WRNMMC, DoD-VA Extremity Trauma & Amputation Center of Excellence
Nearest person month worked:	11 months
Contribution to Project:	Alison is a research physical therapist at WRNMMC, has expertise in physical therapy research, provided input on

study protocol and design, and will assist with subject visits, functional assessments, and training PT personnel.

Name: Shannon M. Lynch, PT, DPT, OCS
LTC, SP
Project Role: Associate Investigator, Physical Therapist & Service Chief at WRNMMC
Nearest person month worked: 12 months
Contribution to Project: LTC Lynch is a physical therapist and service chief at WRNMMC, has expertise in physical therapy research, provided input on study protocol and design, and will assist with subject visits, functional assessments, and training PT personnel.

Name: Michael Stidham, PT
Project Role: Associate Investigator & Physical Therapist at WRNMMC
Nearest person month worked: 5 months
Contribution to Project: Michael is a physical therapist at WRNMMC, has experience in physical therapy research, provided input on study protocol and design, and will assist with subject visits and functional assessments.

Name: Caitlin Mahon, MS
Project Role: Research Biomedical Engineer at WRNMMC, DoD-VA Extremity Trauma & Amputation Center of Excellence
Nearest person month worked: 3 months
Contribution to Project: Nanc has performed work as a research coordinator at WRNMMC, facilitated communications between investigators, assisted with the protocol, CRFs, notes and reports.

Name: Nancy Lee
Project Role: Research Associate / Coordinator at WRNMMC
Nearest person month worked: 12 months
Contribution to Project: Nancy Lee has performed work as a research coordinator at WRNMMC, facilitated communications between investigators, assisted with the protocol, CRFs, notes and reports.

Name: Katherine Ordonio
Project Role: Clinical Research Specialist / Coordinator at MST
Nearest person month worked: 2 months
Contribution to Project: Katherine Ordonio has performed work as a research coordinator at MST, facilitated communications between investigators, assisted with the protocol and CRFs.

Name: Linzie Wagner
Project Role: Grants and Contracts Manager at the Geneva Foundation
Nearest person month worked: 12 months
Contribution to Project: Linzie Wagner has performed work as a grants and

contracts manager at the Geneva Foundation, managed budgets, executed subcontracts, facilitated communications between investigators and submitted reports.

Name: Daisy Schlessinger
Project Role: Lead Data Manager/Project Manager at STATKING Clinical Services
Nearest person month worked: 2 months
Contribution to Project: Daisy Schlessinger has performed work providing clinical data and monitoring expertise at STATKING Clinical Services.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There has been a change in PI that occurred in Year 1, Quarter 4. Principal Investigator, CAPT Mark Fleming, received a transfer within the Navy to the University of Southern California and left Walter Reed National Military Medical Center effective September 2015. A request to change the PI on this award from CAPT Fleming to LTC Leon Nesti was submitted on 25 August 2015 to the sponsor. LTC Nesti is a hand and upper extremity orthopedic reconstructive surgeon at WRNMMC, Associate Professor and Chief of Clinical and Experimental Orthopaedics at Uniformed Services University. Dr. Nesti's current and past clinical and research experience is well-suited for this trial and a smooth transition is anticipated. Dr. Nesti's Bio, CV, and Support documents are attached for reference (see Appendix A-C).

Associate Investigator, CDR Ian Valerio, left Walter Reed National Military Medical Center effective December 2014 and transitioned from Navy active duty to Navy reserves.

Initial PI, Abram Janis, left the project and transferred the PI to CDR Mark Fleming in December 2014. A request to change the PI this award from Mr. Janis to CDR Fleming was submitted on 05 December 2014 to the sponsor. Mr. Janis provided a letter of support and relinquishment as PI and CDR Fleming provided the signed PI Safety Assurance. Approval for the modification requesting the change of PI was received on 28 January 2015.

What other organizations were involved as partners?

Organization Name: The Geneva Foundation

Location of Organization: 917 Pacific Ave, Suite 600 Tacoma, WA 98402

Partner's contribution to the project: Financial support (i.e. grants and contracts management)

Organization Name: R Adams Cowley Shock Trauma Center (STC), University of Maryland Medical Center

Location of Organization: 22 S. Greene Street, Baltimore, MD 21201

Partner's contribution to the project: Facilities (i.e. external site - subaward was submitted to MST on 03 December 2014 and was executed on 15 April 2015); Collaboration (i.e. partner's staff work with project staff on the project); Personnel exchanges (i.e. project staff will work with partner's staff at external site)

Organization Name: STATKING Clinical Services

Location of Organization: 759 Wessel Drive, Fairfield, OH 45014

Partner's contribution to the project: Collaboration (i.e. partner's staff work with project staff on the project); Clinical Monitoring & Data Management

Organization Name: Cook Biotech, Inc.

Location of Organization: 1425 Innovation Place, West Lafayette, IN 47906

Partner's contribution to the project: Vendor (Instructions For Use (IFU) for Biodesign® Plastic Surgery Matrix was obtained from Cook® Medical on 07 May 2015)

5. SPECIAL REPORTING REQUIREMENTS: None

APPENDICES:

- **Appendix A: Dr. Nesti's Bio**
- **Appendix B: Dr. Nesti's CV**
- **Appendix C: Dr. Nesti's Support**



LTC Leon Nesti, MD, PhD: Dr. Leon Nesti received his BS from the United State Military Academy at West Point, and his MD PhD through the clinician-scientist training program at Thomas Jefferson University and Jefferson Medical College. After completing his Orthopaedic Surgery residency at Walter Reed Army Medical Center, Dr. Nesti continued his subspecialty training in Hand and Upper Extremity Reconstructive Surgery in the combined Walter Reed, Curtis National Hand Center program. Dr. Nesti served as the Chief of the Orthopaedic Research Group at the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases and now serves as the Chief of Clinical and Experimental Orthopedics Laboratory at the Uniformed Services University of the Health Sciences. He is a Hand and Upper

Extremity Reconstructive surgeon at Walter Reed National Military Medical Center and performs duties as the Co-Surgical Chief of the Walter Reed Peripheral Nerve Clinic and the Upper Extremity consultant for the United States Military Academy and its athletic teams. He is an active participant in the Army's PROFIS system and recently returned from Afghanistan where he functioned as the 936 Forward Surgical Team's Orthopaedic Surgeon. Dr. Nesti's clinical and scientific interests are focused on progenitor cell function in musculoskeletal disease and regeneration.

Curriculum Vitae
Leon J. Nesti, MD PhD
LTC, MC
(July 2015)



**CONTACT
INFORMATION**

	<i>Work</i>
	Uniformed Services University "America's Medical School" 4301 Jones Bridge Road Bethesda, MD 20814 (240) 994-7347 (Fax) (301) 295-3157 leonnesti@gmail.com leon.j.nesti.mil@mail.mil leon.nesti@usuhs.edu

EDUCATION

BACHELOR OF SCIENCE (ACS CHEMISTRY) – 1995
United States Military Academy, West Point, New York

DOCTOR OF MEDICINE – 2002
Jefferson Medical College of Thomas Jefferson University
Philadelphia, PA

DOCTOR OF PHILOSOPHY – 2000
College of Graduate Studies of Thomas Jefferson University

**PROFESSIONAL
SOCIETIES**

Association of Graduates, United States Military Academy – 1995
American Society of Cell Biology – 1998 to Present
Orthopaedic Research Society – 2001 to Present
Society of Military Orthopaedic Surgeons – 2001 to Present
American Military Surgeons of the United States – 2002
American Academy of Orthopaedic Surgery - 2012 to Present

American Society for Bone and Mineral Research – 2003 to Present
American Society for Surgery of the Hand – 2013 to Present
American Orthopaedic Association -- 2015 to Present

CERTIFICATION AND TRAINING Master Fitness Trainer – 1995
NAUI Dive Certification – 1995
Basic Life Support – 2001
Advanced Cardiac Life Support - 2001
USMLE Steps I-III Pass
ABOS Diplomate 2012

Appointments

Program Director, Walter Reed Section
Combined Walter Reed/Curtis National Hand Center Hand Fellowship
Walter Reed National Military Medical Center
Bethesda, MD May 2015-Present

Chief, Clinical and Experimental Orthopaedics
Department of Surgery
Uniformed Services University of the Health Sciences
Bethesda, MD Oct 2014-Present

Chief, Clinical and Experimental Orthopaedics
National Institute of Arthritis, and Musculoskeletal & Skin Diseases
National Institutes of Health
Bethesda, MD Aug 2009-2014

Associate Professor
Department of Surgery
Uniformed Services University of the Health Sciences
Bethesda, MD February 2014- Present

Assistant Professor
Department of Surgery
Uniformed Services University of the Health Sciences
Bethesda, MD February 2005-2014

Special Volunteer
National Institute of Arthritis, and Musculoskeletal & Skin Diseases
National Institutes of Health
Bethesda, MD June 2004-2009

Guest Investigator
NMRC
Silver Spring, MD January 2005- 2008

Clinical Instructor
Uniform Services University of the Health Sciences
Bethesda, Maryland October 2002- 2005

POSITIONS

Billeted Faculty
Department of Surgery
Uniformed Services University of the Health Sciences
Bethesda, MD
Aug 2011-Present

Adjunct Principle Investigator
National Institute of Arthritis, and Musculoskeletal & Skin
Diseases
National Institutes of Health
Bethesda, MD
Aug 2009-2014

Hand and Upper Extremity Reconstructive Surgeon
United States Military Academy at West Point
Aug 2010-Present

Hand and Upper Extremity Reconstructive Surgeon
Kimbrough Ambulatory Care Center
Ft. Meade, MD
October 2010 - Present

Hand and Upper Extremity Reconstructive Surgeon
Walter Reed National Military Medical Center
Bethesda, MD
October 2010 - Present

Hand and Upper Extremity Reconstructive Surgeon
McDonald Army Health Clinic
Ft. Eustis, VA
Aug 2009-Aug 2011

Hand and Upper Extremity Reconstructive Surgery Fellow
Curtis National Hand Center, Baltimore, MD
Walter Reed Army Medical Center, Washington, DC
Aug 2008-Aug 2009

Orthopaedic Surgery Resident
Walter Reed Army Medical Center
Washington, D.C. June 2002-June 2008

Postdoctoral Fellow
National Institutes of Health
National Institutes of Arthritis, musculoskeletal and skin Diseases
Cartilage Biology and Orthopaedics Branch
Washington, D.C. June 2004-June 2005

Graduate Student, Doctor of Medicine
Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania, August 1995 – June 2002

Graduate Student, Doctor of Philosophy
College of Graduate Studies of Thomas Jefferson University
Philadelphia, Pennsylvania, August 1995 – June 2002

Cadet, United States Military Academy
West Point, New York, July 1991 – June 1995

MILITARY EXPERIENCE

Education: Captain's Career Course - 2010
Combat Casualty Care Course- 2002
AMEDD Officer Basic Course – 1996

Awards: National Defense Service Medal
Army Service Ribbon
Army Achievement Medal
Army Commendation Medal
Global War on Terrorism
NATO Medal
Afghanistan War Medal

Deployment: 936th Forward Surgical Team, Meymaneh, Afghanistan
2011

AWARDS

United States Bone and Joint Decade Young Investigator Award 2007.

Society of Military Orthopaedic Surgeons, Founder's Award 2006.
“Activin Receptor Expression in Heterotopic Ossification”

Washington Orthopaedic Society Resident Research Award, 2005. Nesti LJ, Li WJ, Freedman BA, Shanti RM, Jiang YG, Kuklo TR, Tuan RS. “The Potential of a Novel Hyaluronic Acid Nanofibrous Scaffold (HANFS) Amalgam in Intervertebral Disc Tissue Engineering.”

Huffnagel Award, U.S. Army Basic Science Research Award, 2005. Nesti LJ, Li WJ, Freedman B, Jiang Y, Kuklo TR, Tuan RS. “Novel Tissue Engineered Intervertebral Disc Construct Supports Stem Cell Growth and Differentiation.”

AAOS/OREF Clinician Scientist Development Award, 2005.

Hyman Menduke Research Prize. Recognition for outstanding Research performed while a medical student at Jefferson Medical College. June 2002

New Investigator Recognition Award (NIRA). Orthopaedic Research Society 48th annual meeting, February 2002.

Army Health Profession Scholarship (HPSP)
Tuition, supplies, and stipend support for studies leading to a M.D. degree. 1995-2002

Office of the Dean Travel Award: 2000 – Thomas Jefferson University. Presented to a deserving medical student who has had his research accepted for presentation at a national meeting.

Jefferson Alumni Travel Award: 1999 – Thomas Jefferson University. Presented to a deserving graduate student who has had his research accepted for presentation at a national meeting.

GRANTS/FUNDING

Clinical Evaluation of Decellularized Nerve Allograft with Autologous Bone Marrow Stem Cells to Improve Peripheral Nerve Repair and Functional Outcomes CDMRP, MR140132 2015-2018 (PI - \$2,500,000)

Early Identification of Molecular Predictors of Heterotopic Ossification following Extremity Blast Injury: Animal Model Correlation with Human Disease. CDMRP, OR120071P1. 2013-2016. (Partnering-PI - \$450,000)

Mesenchymal Progenitor Cell Therapy in the Prevention of Tissue Fibrosis, DMRDP, D10-I-AR-J8-981 2011-Present. (PI - \$750,000)

Virtual Stress Test of Healing Fractures, G190VV USAMRRA 2010-2014 (PI – \$110,000)

Stem Cell Based Neurotrophic Enhancement of an Aligned Nanofiber Scaffold for Nerve Repair USAMRAA 304914-1-63348 2011-2014 (PI – \$313,643).

Mechanisms of Heterotopic Ossification. National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases. ZIA AR041191 2009-present.

Congressionally Directed Medical Research Program “Small Molecule Therapy in the Prevention of Heterotopic Ossification” 00519318 , 2009-2010, (PI- \$150,000).

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ABSTRACT PUBLICATIONS

1. Jones PE, Bharmal H, Ji Y, Christopherson G, Hall D, Nesti LJ. Microstructure Of Traumatized Muscle From Blast Injuries Enhances Osteogenesis. 60th Annual Meeting of the ORS, March 15-18, 2014, New Orleans, LA.
2. Jones PE, Bharmal H, Ji Y, Christopherson G, Hall D, Jackson WM, Robertson A, Pellegrini VD, Nesti LJ. Clinical Validation Of An In Vivo Rat Model For The Study Of Blast-induced Heterotopic Ossification. 60th Annual Meeting of the ORS, March 15-18, 2014, New Orleans, LA
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8. Bharmal H, Christopherson G, Ji Y, Cirino C, Jackson W, Nesti L. An Innovative Culture System to Study Heterotopic Ossification. Virginia Orthopaedic Society, May 2013, Washington DC
9. Shin E, Ji Y, Christopherson G, Bharmal H, Jackson W, Nesti L. An In Vitro Fibroproliferative Model to Investigate Cellular Precursors of Heterotopic Ossification. Virginia Orthopaedic Society, May 2013, Washington DC
10. Shin E, Ji Y, Christopherson G, Bharmal H, Jackson W, Nesti L. An In Vitro Fibroproliferative Model to Investigate Cellular Precursors of Heterotopic Ossification. American Academy of Orthopaedic Surgeons, March 2013, Chicago IL
11. Bharmal H, Christopherson G, Ji Y, Cirino C, Jackson W, Nesti L. An Innovative Culture System to Study Heterotopic Ossification. Orthopaedic Research Society, January 2013, San Antonio TX
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15. Bell S, Ji Y, Lopez MP, Nesti LJ. Heterotopic Ossification: Determining the Significance of TGFB1/TGFB3 Ratio. 2012 NIH Summer Poster Day, August 9th, in the Natcher Conference Center #434.
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41. Steinbeck MJ, Nesti LJ, Sharkey PF, Parvizi J. 2006 Myeloperoxidase and Chlorinated-peptides in Osteoarthritis: Potential Biomarkers of the Disease. American Society of Bone and Mineral Research (ASBMR).
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 49. Kuklo TR, Potter BK, Lenke LG, Nesti LJ 2005 Thoracic Vertebral Rotation in Adolescent Idiopathic Scoliosis: What is the Best Plain Radiographic Correlate of Postoperative Derotation? Soc Mil Orthop Surg.
 50. Nesti LJ, Caterson EJ Wang M, Chang R, Chapovsky F, Hoek JB, Tuan RS 2002 TGF- β 1 Intracellular Signaling: Crosstalk Between Intracellular Calcium and MAPK. Trans ORS 48:322.
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PODIUM PAPER PRESENTATIONS

1. Shin E, Ji Y, Christopherson G, Bharmal H, Jackson W, Nesti L. An In Vitro Fibroproliferative Model to Investigate Cellular Precursors of Heterotopic Ossification. Maryland Orthopaedic Association, April 2013, Baltimore MD
2. Bharmal H, Christopherson G, Ji Y, Cirino C, Jackson W, Nesti L. An Innovative Culture System to Study Heterotopic Ossification. Maryland

Orthopaedic Association, April 2013, Baltimore MD *Recognized for 1st place Resident Research Award

3. Shin E, Ji Y, Christopherson G, Bharmal H, Jackson W, Nesti L. An In Vitro Fibroproliferative Model to Investigate Cellular Precursors of Heterotopic Ossification. Society of Military Orthopaedic Surgeons, December 2012, Naples FL
4. Nesti LJ, Ji Y, Christopherson GT, Hall D, Vogler J, Kluk MW, Shin EH, Jackson WM, Nesti LJ. *The Pathophysiology of Heterotopic Ossification: Dysregulation of Tissue Repair and Regeneration*. Trans Orthopaedic Research Society Annual Conference 2012. San Francisco, CA.
5. Ji Y, Shin EH, Vogler J, Kluk MW, Jackson WM, Nesti LJ. Finding Molecular Targets of Heterotopic Ossification Following War Trauma Using microRNA. Trans Orthopaedic Research Society Annual Conference 2012. San Francisco, CA.
6. Jackson WM, Hoover JB, Aragon AB, Onodera J, Nesti LJ, Tuan RS. *Progenitor Cells Harvested from Human Muscle Exhibit Enhanced Osteogenic Potential Following Traumatic Injury*. **Trans. Orthopaedic Research Society Annual Conference 2009**. Las Vegas, NV, #170
7. Onodera J, Jackson WM, Aragon AB, Nesti LJ, Tuan RS. *Heterotopic Ossification Within Injured Muscle: Localizing the Expression of Osteogenic Genes*. **Trans. Orthopaedic Research Society Annual Conference 2009**. Las Vegas, NV, #354
8. Nesti LJ, Li WJ, Freedman BA, Shanti RM, Jiang YG, Kuklo TR, Tuan RS. 2005 *The Potential of a Novel Hyaluronic Acid Nanofibrous Scaffold (HANFS) Amalgam in Intervertebral Disc Tissue Engineering*. **Washington Orthopaedic Society**.
9. Nesti LJ, Li WJ, Freedman B, Jiang Y, Kuklo TR, Tuan RS. 2005 *Novel Tissue Engineered Intervertebral Disc Construct Supports Stem Cell Growth and Differentiation*. **Uniformed Services University for the Health Sciences Surgical Associates Society**.
10. Freedman BA, Potter BK, Nesti LJ, Cho T, Kuklo TR 2005 *Osteoporosis and Distal Radius Fractures: Continued Missed Opportunities* **Amer Acad Orthop Surg**.
11. Nesti LJ, Caterson EJ, Wang M, Chang R, Chapovsky F, Hoek JB, Tuan RS 2001 *TGF- β 1 Signaling Mechanics in Human Osteoblasts*. **Soc Mil Orthop Surg** 43:25.
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INVITED LECTURES

1. Nesti LJ, Murphy KP 2005 *Musculoskeletal Knee and Joint Conditions*. **American College of Occupational and Environmental Medicine (ACOEM)** Washington, DC, USA.
2. Nesti LJ, Li WJ, Shanti RM, Tuan RS. 2005 *Novel Nanofibrous Constructs in Orthopaedic Tissue Engineering*. **Regenerative Medicine Institute (REMEDI), National University of Ireland** Galway, Ireland.
3. Nesti LJ, 2005 *Heterotopic Ossification in Orthopaedic Trauma*. **Regenerative Medicine Institute (REMEDI) Grand Rounds, National University of Ireland** Galway, Ireland.
4. Nesti LJ, 2006 The Stem Cell in Spine Surgery. **American College of Spine Surgeons** Boulder, CO, USA.
5. Nesti LJ, 2007 Stem Cells in Spine Surgery. **American College of Spine Surgery, Nashville, TN, USA.**
6. Nesti LJ, 2010 Progenitor Cells in their Traumatic Niche. 20-21 Oct 2010 **Conference on Human Cell Transformation: Role of Stem Cells in the Microenvironment. McGill University, Montreal, CA.**
7. Nesti LJ, 2011 Muscle Injury, Repair and Regeneration **Quality of Healing: Defining and Quantifying Healing. Brigham and Womens Hospital, Harvard Medical School, Boston, MA.**
8. Nesti LJ, 2011 Initial Management of the Mangled Hand **Orthopaedic Surgery Grand Rounds, Mayo Clinic, Rochester, MN.**
9. Nesti LJ, 2011 Post-Traumatic Heterotopic Ossification **Orthopaedic Research Grand Rounds, Mayo Clinic, Rochester, MN.**
10. Nesti LJ, 2012 Cellular and Molecular Mechanisms of Heterotopic Ossification **Uniformed Services University Surgical Associates Day, Bethesda, MD.**
11. Nesti LJ, 2012 Initial Management of the Mangled Hand and Basic Science Investigation of Tissue Repair and Regeneration. **Brigham and Women's Hospital Grand Rounds, Harvard Medical School, Boston, MA.**

BOOK CHAPTERS

1. Nesti LJ, Kuklo TR, Caterson EJ "Cells, Signals, and Scaffolds: The Future of Spinal Fusion", 2003 In *Advances in Spinal Fusion: Molecular Science, Biomechanics, and Clinical Management*, edited by K Lewandroski, DL Wise, DJ Trantolo, MJ Yaszemski, AA White , 649-668, New York:Marcel Dekker Inc.
2. Ji Y, Christopherson G, Kluk M, Amrani O, Jackson WM, Nesti LJ "Heterotopic Ossification Following Musculoskeletal Trauma: Modeling Stem and Progenitor Cells in their Microenvironment" 2011 In *Human Cell Transformation*.

3. Vogler J, Jackson WM, Nesti LJ “Tissue Engineering and Regeneration” 2011 in Combat Orthopaedic Surgery: Lessons Learned in Iraq and Afghanistan.
4. Freedman BA, Nesti LJ “Management of Complex Combat-Related Soft Tissue Wounds/Negative Pressure Wound Therapy” 2011 in Combat Orthopaedic Surgery: Lessons Learned in Iraq and Afghanistan.
5. Nesti LJ, Wolf JM, Shin EH “Elbow, Wrist and Hand Injuries” 2015 in Musculoskeletal Injuries in the Military

Professional Society Activities

1. Moderator, Growth Factors, 49th Annual Meeting of the Orthopaedic Research Society 2003.
2. Scientific Abstract Reviewer, 51st Annual Meeting of the Orthopaedic Research Society 2005.
3. Moderator, Stem Cells, 51st Annual Meeting of the Orthopaedic Research Society, 2005.
4. Scientific Abstract Reviewer, 52nd Annual Meeting of the Orthopaedic Research Society 2006.
5. Moderator, Intervertebral Disc, 52nd Annual Meeting of the Orthopaedic Research Society 2006.
6. Grant Reviewer, Musculoskeletal Transplant Foundation 2007.
7. Manuscript Reviewer Journal of Immunopharmacology 2007 - Present.
8. Manuscript Reviewer Journal of Orthopaedic Research 2007 - Present.
9. Orthopaedic Research Society, Media Relations Committee 2010-2014.
10. ASSH Research Management Committee. 2010-2014.
11. Chair, ASSH Research Management Committee 2014-Present
12. Scientific Reviewer, Congressionally Directed Medical Research Programs, 2010- Present.
13. Scientific Reviewer, Armed Forces Institute of Regenerative Medicine II. Fall 2012.
14. Manuscript Reviewer PLOS One 2014-Present

USUHS Activities

1. 27 March 2005, Orthopaedic Orientation Class.
2. 2003-2008, Orthopaedic Pearls Class (provided to 3rd and 4th year medical students during their Orthopaedic rotations)
3. April 2007 – Present, Mentor Orthopaedic Research Lab
4. December 2007, Introduction to Orthopaedic Physical Exam.
5. Co-Director USUHS Microvascular Surgery Course 2012-Present.
6. Space Committee Member 2014-Present

PATENTS

1. Tuan RS, Caterson EJ, Li WJ, Nesti LJ 2001 *Bio-reasorbable Polymer/Alginate Amalgam Cell Construct for Cartilage Tissue Engineering* Provisional Patent Application. Registration #: 42,215 Docket # TUA 01-P0002.
2. Li WJ, Nesti LJ, Tuan RS 2006 *Cell-Nanofiber Composite and Cell-Nanofiber Composite Amalgam Based Engineered Intervertebral Disc*. DHHS Reference No. E-309-2006/1, U.S. Provisional Application No. 60/848,284 filed 28 Sep 2006
3. Nesti LJ, Jackson WM, Tuan RS. *A nanofibrous conduit seeded with muscle-derived mesenchymal progenitor cells as trophic mediators for peripheral nerve regeneration*. November 26, 2008, US 8,652,458 B2

Previous, Current, and Pending Support

Previous Support

PI: Dr. Leon Nesti

Title: Mechanism of in the Military Amputee Population

Time Commitment:

Supporting Agency: Military Amputee Research Program, Walter Reed Army Medical Center

Funding Agency's Procuring Contracting/Grants Officer:

Performance Period: 2006 - 2008

Level of Funding: \$600,000

Project Goal:

Role: PI

PI: Dr. Leon Nesti

Title: A Novel Biomimetic Allograft Bone Powder-Nanofibrous Scaffold Bone Substitute

Time Commitment:

Supporting Agency: Musculoskeletal Transplant Foundation

Funding Agency's Procuring Contracting/Grants Officer:

Performance Period: 2007-2008

Level of Funding: \$120,000

Project Goal:

Role: PI

PI: Dr. Leon Nesti

Title: Evaluation of a Nanoscale Peripheral Nerve Conduit

Time Commitment:

Supporting Agency: Comprehensive Neuroscience Program

Funding Agency's Procuring Contracting/Grants Officer:

Performance Period: 2008 - 2010

Level of Funding: \$300,000

Project Goal:

Role: PI

PI: Dr. Leon Nesti

Title: Small Molecule Therapy in the Prevention of Heterotopic Ossification

Time Commitment: 0.6 calendar months

Supporting Agency: DRMRP

Funding Agency's Procuring Contracting/Grants Officer:

Sudha Srinagesh

Vice President for Research Administration Services

Henry M. Jackson Foundation

1401 Rockville Pike, Suite 600

Rockville, MD 20852-1402

(301) 294-1276

ospnga@hjf.org

Performance Period: 2009 - 2010

Level of Funding: \$150,000

Project Goal: The aim of this project is to test the hypothesis that treatment with Dorsomorphin will make up for failures in endogenous BMP signaling attenuation mechanisms that occur in the traumatically injured muscle and lead to heterotopic ossification.

Role: PI

PI: Dr. Leon Nesti

Title: Virtual Stress Test of Healing Fractures

Time Commitment:

Supporting Agency: USAMRRA

Funding Agency's Procuring Contracting/Grants Officer:

Performance Period: 2010-2014

Level of Funding: \$110,000

Project Goal:

Role: PI

PI: Dr. Leon Nesti

Title: Stem Cell Based Neurotrophic Enhancement of an Aligned Nanofiber Scaffold for Nerve Repair

Time Commitment: 1.2 calendar months

Supporting Agency: USAMRAA

Funding Agency's Procuring Contracting/Grants Officer:

Thomas Scofield

Vice President Business Development

Henry M. Jackson Foundation

1401 Rockville Pike, Suite 600

Rockville, MD 20852-1402

(301) 294-1243

tscofield@hjf.org

Performance Period: 2011-2014

Level of Funding: \$313,643

Project Goal: The goal of this project is to test the hypothesis that mesenchymal progenitor cells derived from traumatized muscle and seeded within a biodegradable scaffold consisting of aligned nanofibers are capable of providing neurotrophic enhancement of nerve regeneration by generating a biochemical bridge that promotes axonal growth and migration of cells that promote regeneration.

Role: PI

Current Support

PI:

Title: Mechanisms of Heterotopic Ossification.

Time Commitment:

Supporting Agency: NIH

Funding Agency's Procuring Contracting/Grants Officer:

Performance Period: 2009 - Present

Level of Funding:

Project Goal:

Role:

PI: Dr. Leon Nesti

Title: Mesenchymal Progenitor Cell Therapy in the Prevention of Tissue Fibrosis

Time Commitment: 2 calendar months

Supporting Agency: DMRDP

Funding Agency's Procuring Contracting/Grants Officer:

Robyn Strachan

Budget Officer

National Institute of Arthritis and Musculoskeletal and Skin Diseases
Office of the Director
31 Center Drive
Bethesda, MD 20892-2350
(301) 496-5521
strachar@mail.nih.gov

Performance Period: 2011-Present

Level of Funding: \$750,000

Project Goal: The goal of this project is to test the hypothesis that autologous MPCs derived from traumatically injured muscle are a safe, effective and convenient cell type for cell-based therapy to prevent scar tissue formation following trauma-related orthopaedic injury.

Role: PI

PI: Dr. Leon Nesti

Title: Early Identification of Molecular Predictors of Heterotopic Ossification following Extremity Blast Injury: Animal Model Correlation with Human Disease

Time Commitment:

Supporting Agency: CDMRP

Funding Agency's Procuring Contracting/Grants Officer:

Performance Period: 2013 - 2016

Level of Funding: \$450,000

Project Goal:

Role: Partnering PI

PI: Dr. Leon Nesti

Title: Instructive Biologic Scaffold for Functional Tissue Regeneration Following Trauma to the Extremities

Time commitments: 1.2 Calendar Months

Supporting Agency: CDMRP

Name/Address of the Funding Agency's Procuring Contracting/Grants Officer: N/A

Performance Period: 9/3/2014-8/31/2017

Funding: \$1,487,923.08

Goal: The proposed clinical trial will establish the effectiveness of a UBMECM scaffold for the restoration of functional skeletal muscle tissue, including the restoration of blood supply and innervation. Successful completion of our objectives would provide a regenerative alternative to the current standard of care for extremity VML and restore quality of life to injured war fighters. We hypothesize that subjects who receive the UBM-ECM scaffold in the acute and subacute post-injury periods will have significant new muscle growth and improvements in strength in the treated extremity.

List of Specific Aims:

Specific Aim 1: To induce the de novo formation of at least 25% of the missing muscle tissue using UBM- ECM.

Specific Aim 2: To restore at least 25% of the function of the involved muscle group.

Role: Co-Principal Investigator

PI: Dr. Leon Nesti

Title: Dermal Coverage of Traumatic War Wounds

Time Commitment: 1.2 calendar months

Supporting Agency: CDMRP

Name and Address of Funding Agency's Procuring Contracting/Grants Officer:

Sandra Rosario

U.S. Army Medical Research Acquisition Activity Grant Specialist - Gold Team

843 Chandler Street

Fort Detrick, MD 21740

T: 301-619-4063

sandra.rosario@amedd.army.mil

Performance Period: 10/31/2012-10/30/2016

Funding: \$1,414,865

Goal: The goal of the study described herein is to determine the effectiveness of the use of the ReCell device over a widened STSG mesh in combination with INTEGRA will improve upon the current standard of care.

List of Specific Aims:

- Specific Aim 1: Assess the preliminary effectiveness of ReCell treatment of full-thickness wounds treated with INTEGRA MBWM compared to a control site.
- Specific Aim 2: Assess the long-term effectiveness of ReCell treatment of full-thickness wounds treated with INTEGRA MBWM compared to a control site.
- Specific Aim 3: Evaluate safety of ReCell treatment of full-thickness wounds treated with Integra MBWM compared to control site.

Role: Principal Investigator

Scientific/Budgetary Overlap: None

Pending Support

PI: Dr. Leon Nesti

Title: Clinical Evaluation of Decellularized Nerve Allograft with Autologous Bone Marrow Stem Cells to Improve Peripheral Nerve Repair and Functional Outcomes

Time Commitment:

Supporting Agency: CDMRP

Funding Agency's Procuring Contracting/Grants Officer:

Performance Period: 2015 - 2018

Level of Funding: \$2,500,000

Project Goal:

Role: PI