AWARD NUMBER: W81XWH-16-2-0067

TITLE: Extremity Regeneration of Soft Tissue Injury Using Growth Factor-Impregnated Gels

PRINCIPAL INVESTIGATOR: Simon Talbot, MD

CONTRACTING ORGANIZATION: Brigham and Women's Hospital

REPORT DATE: October 2019

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

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Oct 2019	Annual	30Sep 2018 -29 Sep 2019

4. TITLE AND SUBTITLE
Extremity Regeneration of Soft Tissue Injury Using Growth Factor-Impregnated Gels

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-2-0067

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Simon Talbot, MD., Sarah Kinsley PA-C

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Brigham and Women's Hospital
Boston, Massachusetts 02115

8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Materiel Command
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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

Nearly all experiments have been completed and a no cost extension has been approved in order to complete all planned surgeries. A final surgery is scheduled for November, 2019 to determine function of VEGF and VEGF + IGF1 in an ischemic-only injury. All other experiments to evaluate the dose-response relationship, determine function of growth factor on nerve regeneration and function of each growth factor on independent nerve versus ischemic injuries have been completed. There has been ongoing research and development on the alginate gels and growth factors through collaboration with the Wyss Institute. We have been approved to revise our statement of work, eliminating the pilot non-GLP studies. We are completing 4 GLP toxicity studies through an outside vendor with the Wyss Institute.

15. SUBJECT TERMS Nerve and vessel regeneration. Growth factor: VEGF and IGF.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	Unclassified	49	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The overarching, long-term goal of this project is to develop technologies that maximize restoration of severely injured limbs by restoring muscle and nerve functions and avoiding amputation. This research specifically focuses on promoting regeneration of the injured host tissue by use of exogenous growth factors. A natural soft polymer gel material, alginate, has been fabricated to release two natural growth factors – vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1). Repeated injections of growth factor-alginate material are performed following a surgically induced traumatic ischemic injury and followed with muscle biopsies and nerve conduction studies to track regeneration. Preliminary results from small animal studies show that this approach can promote expansion of the host cells, and enhance restoration of blood flow, regeneration of muscle tissue, and reconnection of nerves. Currently, this project is being tested in a large animal swine model for its effectiveness in restoring blood flow, muscle and nerve tissue, and connection of nerve to muscles. The project will extend development of the injectable gel into a prototype product, suitable for commercialization.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Vascularized endothelial growth factor (VEGF)
Insulin-like growth factor-1 (IGF-1)
Alginate gel
Ischemia-reperfusion
Large animal model

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Subtask	Timeline in Months	Completion
Subtask 1.1: Submission of IACUC protocol for Aims 1 and 2	1-4	Completed
Subtask 1.2: Process and method development product	1-8	Completed
Subtask 1.3: Development of a large animal model	4-8	Completed
Subtask 1.4: Development of assays (histology), functional studies (walking) and electrophysiology studies (EMG/NCS)	4-8	Completed
Subtask 1.5: Evaluation of dose-response relationship in limb transection model	8-12	Completed
Subtask 2.1: Determine function of each of VEGF and VEGF+IGF1 on nerve regeneration	12-18	Completed
Subtask 2.2: Determine function of each VEGF and VEGF+IGF1 on ischemia-reperfusion	18-24	Next surgery: Nov, 2019
Subtask 3.1: Method and process qualification	24-36	90%
Subtask 3.2: GLP pharmacology-toxicity studies	20-24	75% (3 of 4 studies complete)
Subtask 3.1: Determine proposed clinical design	24-25	5%
Subtask 3.2: Determined proposed pharmacology-toxicity study design	24-25	5%

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

During the third year of study, accomplishments include completing almost all surgical experiments. Experiments to evaluate the dose-response relationship and determine function of the growth factor on nerve regeneration are complete. A final surgery to evaluate growth factor response in ischemia-reperfusion injury will be complete in November of 2019. This will be the final surgery. We will continue to perform studies every three weeks with EMG, muscle biopsies and functional walking assessments through collaboration with USUHS and the Wyss Institute. The final surgery swine will be followed for 4 months with completion in March, 2020. Following their euthanasia, systematic review and analysis of all data will begin.

The Wyss Institute has continued to refine the alginate manufacturing process and testing methods. Ongoing histopathology processing and interpretation of muscle biopsies continues. This includes evaluation of oxidization, reduction, filtration, sterilization and reconstitution for production of the alginate gel. As the project continues, additional final product assessments will be carried out for cross linking density, sterility, endotoxin and growth factor release of the final product. The Wyss Institute has been instrumental in developing the protocol to process the muscle biopsies that is carried out by USUHS. The protocol continues to be optimized by the BWH Core Laboratory for staining motor endplates.

Through a contracting research laboratory, GLP Toxicity Studies are underway to fulfill criteria requirements for an IND submission. These include four studies: maximization sensitization study in guinea pigs, intracutaneous extraction study in rabbits, acute toxicity study in mice and a 28-day repeated dose toxicity study in rats. The repeated dose toxicity study will be completed in spring, 2020.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of

these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the final months of this project, we will complete the swine surgical experiments to evaluate the growth factor response on ischemia-reperfusion injuries. Following completion of the experiments at 4 months post-operatively in March, 2020, we will begin to analyze the muscle biopsies and histopathology en bloc. We will complete the final GLP toxicity study with the 28-day repeated dose toxicity study in rats and complete our pre-IND to bring to the FDA for further discussion on IND submission.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*

- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report

Several swine have developed insensate limb wound necrosis ultimately resulting in euthanasia. Through discussions with IACUC and veterinary staff, modifications to post-operative care have been instituted. This includes a modified dressing on the insensate limb and padded flooring to minimize traumatic wounds. Additional support staff will be present to monitor swine during the early post-operative period.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Submission of a manuscript discussing our large animal protocol to PLOS One: "A Yorkshire swine (*Sus scrofa domesticus)* model for nerve regeneration and ischemia based on the sciatic nerve and femoral artery". This is currently under editorial review and revision.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

  Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

  Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

- Nothing to report.

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name: Simon Talbot
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 4.8
Contribution to Project: Directs and oversees all phases of the study.

Name: EJ Caterson
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2.4
Contribution to Project: Assistance with planning and surgical aspects of the study.

Name: Sarah Kinsley
Project Role: Research Assistant
Research Identifier:
Nearest person month worked: 24.0
Contribution to Project: Involved in coordination and ensuring each phase of the project remains on schedule, writing protocols, purchasing.

Name: David Mooney
Project Role: Co-Principal Investigator
Research Identifier:
Nearest person month worked: 0.48
Contribution to Project: Involved in management of Wyss Institute input to project.

Name: Ed Doherty
Project Role: Co-Principal Investigator
Research Identifier:
Nearest person month worked: 4.80
Contribution to Project: Involved in coordination of production of Wyss gels.

Name: Alexander Stafford
Project Role: Scientist
Research Identifier:
Nearest person month worked: 4.80
Contribution to Project: Involved in production of gels.

Name: Des White
Project Role: Research Associate
Research Identifier:
Nearest person month worked: 12.0
Contribution to Project: Involved in production of gels.

Name: Tracy Snyder
Project Role: Research Associate
Research Identifier:
Nearest person month worked: 24.0
Contribution to Project: Involved in production of gels.

Name: Leon Nesti
Project Role: Co-Principal Investigator
Research Identifier:
Nearest person month worked: 0.24
Contribution to Project: Involved in management of USUHS staff and laboratory including coordination of animal experimentation on site.

Name: Jody Richardson
Project Role: Research technician
Research Identifier:
Nearest person month worked: 24.0
Contribution to Project: Involved in day-to-day running and local coordination of activities.

Name: Jaira Vasconcellos
Project Role: Staff scientist
Research Identifier:
Nearest person month worked: 12.0
Contribution to Project: Involved in day-to-day running and local coordination of activities.

Name: Amal Nadel
Project Role: Program manager
Research Identifier:
Nearest person month worked: 2.40
Contribution to Project: Involved in coordination of activities through USUHS.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not

necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Please see the attached and updated DoD support forms for Dr. Simon Talbot and Dr. Dave Mooney.

Summary of changes for Dr. Dave Mooney:

- Current: VENTURES – Vision for Excellence of Navajo Technical University in Research and Education in STEM
- i3 Center Biomaterials to Promote T Cell Immunity
- Completed, now previous: A New Platform for Burn Treatment and for Delayed Evacuation of Service Members
- Pending: Novel Mast Cell Stabilizers for Management of the Diabetic Foot Ulceration
- Pending: In situ cell programming scaffolds for potentiating CAR-T cell therapies
- Pending: Fabricating DNA origami with optimal CpG spatial distribution and neoantigens to generate a personalized cancer vaccine towards Th1 polarized immune response.
- Pending: Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center: Advancing Dental, Oral and Craniofacial Regeneration to Clinical Trial Initiation
- Pending: Polymeric Matrices with defined cell adhesion

Summary of changes for Dr. Simon Talbot:

- Current, was pending: A novel approach to upper extremity amputation to augment volitional motor control and restore proprioception
- Current, was pending: T- cells and rejection in vascularized composite allotransplants
- Current: A novel approach to lower extremity residual limb revision to augment volitional motor control, restore proprioception and reverse limb atrophy
- Pending: Use of the Patient Generated Index (PGI) for evaluating patient experience in amputation and reconstruction
- Pending: Core Outcomes in VCA and Extremity Reconstruction (COVER)

Summary of changes for Dr. Leon Nesti:

- Current: Phase 2 Study for Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Use as a Vascular Prosthesis for Femoro-Popliteal Bypass in Patients with Peripheral Artery Disease
- Pending: Electrical Stimulation to Accelerate Nerve Regeneration
- Pending: Optimization and assessment of a biologic to improve functional recovery after peripheral nerve injury

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have

provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization name: United States Uniformed Health Services
Location of Organization: Associated with Walter Reed Military Medical Center in Bethesda, MD
Partner's Contribution to the project: Facilities and collaboration

Organization name: Wyss Institute for Biologically Inspired Engineering
Location of Organization: Associated with Harvard University. Located in Boston, MA
Partner's Contribution to the project: Collaboration and in-kind support developing the alginate and growth factor.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

Extremity Regeneration of Soft Tissue Injury Using Growth Factor Impregnated Gels

Log Number: DM153165
Award Number: W81XWH-16-2-0067

PI: Simon G. Talbot, MD **Org:** Brigham and Women's Hospital **Award Amount:** $2.1 M

Study/Product Aim(s)

Hypothesis: Injection of growth factor impregnated hydrogels can restore blood flow, promote muscle and nerve regeneration, and restore nerve connections to muscle.

• Aims: Evaluate biocompatibility and efficacy of alginate gel-based delivery of VEGF and IGF-1 in a large animal model of limb injury including ischemia-reperfusion and nerve transection-repair in support of future human clinical studies.

Approach

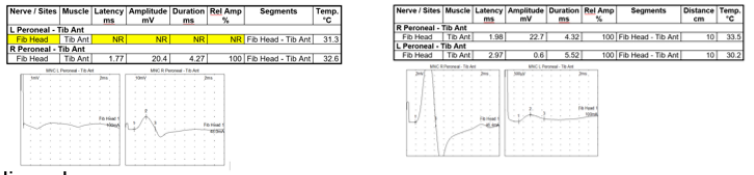
Experiment 1: Determine optimal ischemia time and optimal growth factor dose in large animal model.

Experiment 2: Determine effect of VEGF and IGF-1 on nerve regeneration.

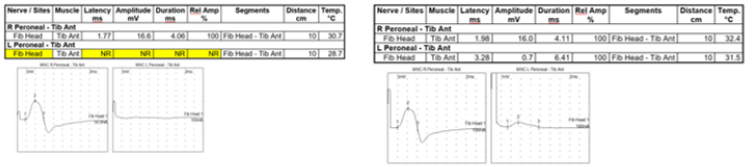
Experiment 3: Determine effect of VEGF and IGF-1 on ischemia-reperfusion.

EMG demonstrated motor response from week 8 to week 11 in the medium and high dose VEGF alginate gel

High dose



Medium dose



Timeline and Cost

Activities	2017	2018	2019
Determine optimal ischemia time and optimal growth factor dose in large animal model.			
Determine effect of VEGF and IGF-1 growth factor on nerve regeneration.			
Determine effect of VEGF and IGF-1 growth factor on ischemia-reperfusion.			
Estimated Budget ($K)	733	702	665

Updated: 10/30/2019

Goals/Milestones

CY17 Goal – Determine optimal ischemia time and growth factor dose
☑Develop large animal model
☑Submit to IACUC and ACURO
☑Begin experiment 1 on 20 animals
☑Modify IACUC protocol to minimize postoperative risks
☑Preliminary testing of alginate gel confirms consistency of product

CY18 Goal – Determine effect of growth factor on nerve regeneration
☑Complete experiments to determine ischemia time
☑Begin dose experiments on 15 animals

CY 19 Goal – Determine effect of growth factor on ischemia-reperfusion
☑Experiment 3
☑Initiate development of IND application to FDA

Comments/Challenges/Issues/Concerns

- Approved no-cost extension to continue moving toward pre-IND meeting

Budget Expenditure to Date

Actual Expenditure: $1,734,429 (direct costs: 1,397,099)

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

- DoD Support document for David Mooney
- DoD Support document for Simon Talbot
- DoD Support document for Leon Nesti

Other Support, MOONEY, DAVID J.

CURRENT

Title: Polymeric Matrices with Defined Cell Adhesion (R01DE013033)
Time Commitment: .43 calendar months
Supporting Agency: National Institutes of Health (NIH/NIDCR)
Name and address of funding agency's Procuring Contracting/Grants Officer: Gabriel Hildago
Email: hidalgoge@nidcr.nih.gov Phone: 301-827-4630
Performance Period: 07/14/14-05/31/20 NCE
Level of Funding: $2,350,405
Brief description of project's goals: The aim of this proposal is to develop materials to enable the regeneration of bony tissues for reconstructive dental and craniofacial applications.
Specific Aims: 1) Fabricate alginate hydrogels that display a range of stress relaxation and creep times ranging from seconds-hours, and characterize the relation between initial moduli, stress relaxation and creep rate and MSC adhesion, proliferation, and differentiation; 2) Quantify the impact of viscoelasticity on established mechanotransduction pathways, including adhesion peptide clustering, integrin-peptide bond formation, intracellular signaling pathways, and cellular traction forces; and 3) Determine if stress relaxation alters the rate and extent of bone formation in vivo from MSCs transplanted in hydrogels of varying initial mechanical properties and rates of stress relaxation.

Title: Hydrogels to promote tendon healing
Time Commitment: 0 calendar months
Supporting Agency: Novartis Pharmaceutical
Name and address of funding agency's Procuring Contracting/Grants Officer: Novartis Institutes for Biomedical Research, Attn: General Counsel, 250 Massachusetts Avenue, Cambridge, MA 02139
Performance Period: 09/01/14-08/31/20
Level of Funding: $1,019,673
Specific Aims: The aim of this project is to develop controlled release polymers for drugs that promote tendon regeneration.

Title: Material Research Science and Engineering Center (MRSEC) (DMR-1420570)
Time Commitment: 0 calendar months
Supporting Agency: National Science Foundation, (PI: Weitz,D.)
Name and address of funding agency's Procuring Contracting/Grants Officer: Daniele Finotello,
DMR Division of Material Research, MPS Director for Mathematical and Physical Science, 4201 Wilson Blvd., Arlington, VA 22230
Performance Period: 11/01/14-10/31/20
Level of Funding: $118,344
Brief description of project's goals: This center identifies new research areas, and trains and retains students in materials science and engineering.

Title: Extremity regeneration of soft tissue injury using growth factor impregnated gels (W81XWH-16-2-0067)
Time Commitment: .12 calendar months
Supporting Agency: Department of Defense
Name and address of funding agency's Procuring Contracting/Grants Officer: Elena G. Howell,
Grants Officer, 820 Chandler Street, Fort Detrick, MD 21702-5014.
Performance Period: 9/30/16-09/29/20 NCE
Level of Funding: $1,014,648
Brief description of project's goals: The Programmable Nanomaterials (PNM) platform of the Wyss Institute for Biologically Inspired Engineering at Harvard University will develop a biomaterial for delivery of growth factors to promote limb regeneration. This project will be a component of a larger collaborative project in which these materials are used in a large animal model (animal work to be done at collaborators lab). The PNM will perform the studies and collect data required to file an IND application with the FDA at the completion of these studies. *Subcontractor to Brigham and Women's Hospital.*

Title: Mechanisms of Prosthetic Arterial Graft Failure (R01HL021796)
Time Commitment: .76 calendar months
Supporting Agency: National Institutes of Health (NIH/NHLBI)
Name and address of funding agency's Procuring Contracting/Grants Officer: Gary H. Gibbons,
M.D., Director of the National Heart Lung and Blood Institute, Building 31, Room 5A52, 31 Center Drive MSC2486, Bethesda, MD 20892.
Performance Period: 02/01/17-01/31/2022
Level of Funding: $980,842
Brief description of project's goals: Dr. Mooney's laboratory will develop the cryogel system for sustained delivery of therapeutic agents from the grafts. The laboratory will design the hydrogels, synthesize and characterize. They will collaborate closely with the LoGerfo laboratory in the animal studies in which these materials are tested. *Subcontractor to Beth Israel Deaconess Medical Center.*

Title: Michigan-Pittsburgh-Wyss Resource Center: Supporting Regenerative Medicine in Dental, Oral and Craniofacial Technologies (U24DE026915) (Kohn, D.)
Time Commitment: 1.20 calendar months
Supporting Agency: NIH/NIDCR
Name and address of funding agency's Procuring Contracting/Grants Officer: Gabriel Hidalgo
hidalgoge@nidcr.nih.gov Phone: 301-827-4630
Performance Period: 3/1/17-2/29/20
Level of Funding: $529,567
Brief description of project's goals: Our project aims to address the problem of dental disease. Dental caries affects 60-90% of school-age children and the vast majority of adults worldwide, which impact long-term oral health causes significant economic impact. Developing reliable and affordable therapeutic strategies for treating dental diseases is an important area of investigation**.**

Supplement: To identify, develop and validate a high-pressure carbon dioxide process to terminally sterilize the final alginate/VEGF/ IGF product.

Title: 3D Models of Immunotherapy (U01CA214369)
Time Commitment: .76 calendar months
Supporting Agency: National Institutes of Health (NIH/NCI)
Name and address of funding agency's Procuring Contracting/Grants Officer: Marianne Galczynski
Email: marianne.galczynski@nih.gov Phone: 240-276-6300
Performance Period: 4/1/17-3/31/22
Level of Funding: $2,957,705
Brief description of project's goals: At the completion of this project we will have developed and thoroughly characterized novel, 3D models of both mouse and human biology that will replicate the vaccination site and vascularized tumors.
Specific Aims: 1) Utilize 3D printing to develop an in vitro model of mouse melanoma incorporating a vascular network that enables long-term perfusion of the tissue and trafficking of immune cells from the vascular component to the tumor stroma; compare the immune modulatory function of these tissues to mouse tumors grown in vivo via both examination of cell surface markers and gene expression; 2) Develop a 3D model of a mouse vaccination site using previously developed 3D biomaterials utilized for
vaccination and mouse immune cells, and compare the ability of vaccines to both mature dendritic cells and the ability of these cells to activate T cells in vitro and in vivo; 3) Create patient-specific human versions of the tumor and vaccine site using vascular, tumor and immune cells derived from the same patient; 4) Utilize the mouse and human vaccine site and tumor models to begin exploring the impact of vaccination at a site distant from the tumor versus intratumoral vaccination, and the role of checkpoint blockade therapy and angiogenic factors on tumor cell-immune cell interactions. *Collaboration with Jennifer Lewis (Harvard/Wyss) and F. Stephen Hodi (DFCI).*

Title: MSC Encapsulations with Thin Gel Coating (R01EB023287)
Time Commitment: .76 calendar months
Supporting Agency: National Institutes of Health (NIH/NIBIB)
Name and address of funding Agency's Procuring Contracting/Grants Officer: Florence Turska
Email: ft7p@nih.gov Phone: 301-496-9314
Performance Period: 9/15/17-6/30/20
Level of Funding: $2,014,692
Brief description of project's goals: Here, we propose to further develop this new technology, and to study its utility in context of hematopoietic stem cell therapy (HSCT). We have put together a unique team to address the hypothesis underlying this project, with leaders in microfluidics technology (Weitz), biomaterials (Mooney), and hematopoietic stem cell (HSC) biology and HSCT (Scadden).
Specific Aims: 1) Tune the chemical and physical properties of microgels (gels encapsulating cells < 5 microns), and scale-up the microfluidics technology to enable clinically relevant numbers of MSCs to be encapsulated with high efficiency; 2) Determine how MSC persistence and paracrine secretions following intravascular transplantation can be tuned by the chemical and

physical properties of the encapsulating alginate hydrogel; 3) Study the impact of microgel-encapsulated MSCs and the alteration of the MSC secretome on the treatment of graft versus host disease (GVHD) following HSCT in a rodent model. *Collaboration with David Weitz (Harvard/SEAS) and David Scadden (MGH).*

Title: Biomaterial Cancer Vaccines that Generate Patient-Specific Antigen In Situ (R01CA223255)
Time Commitment: .76 calendar month
Supporting Agency: National Institutes of Health (NIH/NCI)
Name and address of funding Agency's Procuring Contracting/Grants Officer: Kerry Gastley
Email: kerry.gastley@nih.gov Phone: 240-276-5472
Performance Period: 12/1/17-11/30/22
Level of Funding: $2,024,165
Brief description of project's goals: This project will result in the development of new, patient-specific vaccination strategy that does not require personalized manufacturing.
Specific Aims: 1) Develop cryogels capable of being injected intra and/or peritumorally that recruit dendritic cells (DCs) through GM-CSF release and control the timing of release of nanoparticles (NPs) containing TLR 3, 4 and 9 ligands in order to concentrate and activate APCs within the tumor, and induce their lymph node homing; 2) Determine the impact of localizing immunostimulatory chemotherapeutic agents to tumors on cancer cell death, and determine the impact of combined chemotherapy and vaccination on tumor growth and the tumor-specific host immune response; 3) Examine the ability of vaccination at the primary tumor to yield therapeutic effects on distant tumors in the body, and combine the biomaterial-based vaccine strategy with checkpoint blockade therapy.

Title: Material Engineered Scaffold Vaccines
Time Commitment: 0 calendar months
Supporting Agency: Novartis Institutes for Biomedical Research
Name and address of funding agency's Procuring Contracting/Grants Officer: Novartis Institutes for Biomedical Research, Attn: General Counsel, 250 Massachusetts Avenue, Cambridge, MA 02139
Performance Period: 3/2/18-3/2/20
Level of Funding: $1,500,000
Brief description of project's goals: Research and development of PLG engineered vaccine scaffolds containing autologous tumor necrotic tumor lysate, GM-CSF and Novartis Adjuvants and Novartis Other Molecules up to and including pre-clinical toxicology assessment.
Specific Aims: 1) Develop pre-clinical data to support filing an IND for testing of implantable poly-lactide-co-glycolide (PLG) material engineered scaffold vaccines incorporating Novartis Adjuvants/Controlled Components; 2) Research and develop injectable versions of material engineered scaffold vaccines.

Title: Developing the Captured Antigen Presentation System (CAPS) as vaccine against bovine tuberculosis
Time Commitment: 0 calendar months
Supporting Agency: International Development Research Center

Name and address of funding agency's Procuring Contracting/Grants Officer: Barbara Alves, Grant Administrator, International Development Research Centre, 150 Kent St. Ottowa, ON Canada K1G3H9
Performance Period: 06/01/18-05/31/20
Level of funding: $624,911
Brief description of project's goals: The ultimate aim of the proposed work is to develop an effective, safe and cost-effective vaccine against bovine TB.
Specific Aims: 1) Demonstrate the incorporation of vaccine pathogen candidates (BCG, M. bovis, and/or other captured antigens) in the CAPS vaccine system and evaluate the configurations ability to elicit cell mediated and antibody responses in a mouse non-challenge model; 2) Validation of efficiency of selected vaccine candidates in a cattle vaccination and TB challenge study.

Title: Engineering Skeletal Muscle with Biodegradable Hydrogels (R01DE013349)
Time Commitment: .76 calendar month
Supporting Agency: National Institute of Health (NIH/NIDCR)
Name and address of funding agency's Procuring Contracting/Grants Officer: April Harrison, harrisona@mail.nih.gov, Phone: 301-827-4628, 6701 Democracy Blvd, Bethesda, MD, 20892-4878
Performance Period: 07/06/18-06/30/23
Level of Funding: $3,128,584
Brief description of project's goals: The aims of this proposal are to engineer skeletal muscle by developing biodegradable hydrogels, which mediate transplanted cell population of damaged muscle, in concert with delivery of growth factors that mediate revascularization and reinnervation of the damaged muscle.
Specific Aims: 1) Optimize the regime of mechanical stimulation applied to injured muscle via the development of a new soft robotic system that allows one to simultaneously treat multiple animals in parallel with control over the amplitude, frequency, and duration of stimulation; 2) Delineate the mechanism(s) underlying the mechanically-driven regeneration, focusing on the role of altered transport and immune cells in the damaged tissue; 3) Reconstitute a similar profile of immune cell activity without mechanical stimulation, and study the impact on muscle regeneration.

Title: Alliance for Regenerative Rehabilitation Research and Training Grant (AR3T) (P2CHD086843)
Time Commitment: .12 calendar months
Supporting Agency: Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD) (PI; Ambrosio, F.)
Name and address of funding Agency's Procuring Contracting/grants Officer: Ralph M. Nitkin, PhD, Deputy Director NCMRR, Rockville, MD 20847
Performance Period: 07/30/18-06/30/20
Level of Funding: $116,694 (Harvard subcontract)
Brief description of project's goals: Robotic actuator for in vivo muscle stimulation. Development of a soft robotic device which can deliver various mechanical parameters to severely injured murine skeletal muscle in a controlled manner with adaptability of ultrasound imaging during stimulation. *Subcontractor to University of Pittsburgh*

Title: VENTURES – Vision for Excellence at Navajo Technical University in Research and Education in STEM (DMR-1828012)
Time Commitment: 0 calendar months
Supporting Agency: National Science Foundation (PI: Soundappan/Weitz)
Name and address of funding agency's Procuring Contracting/Grants Officer: Debasis Majumdar
DMR Division Of Materials Research MPS Direct For Mathematical & Physical Science, 4201 Wilson Blvd., Arlington, VA 22230
Performance Period:09/01/18-08/31/23
Level of funding: $0.00
Brief description of project's goals: The goals are to: increase the number of Native Americans earning undergraduate degrees in STEM fields; increase the research infrastructure at Navajo Technical University; increase the number of Native Americans entering and completing graduate programs in materials science and related fields; include Native American perspectives and methods of inquiry in materials science research.
Specific Aims: The three research areas of the PREM apply materials research to issues that are of importance to the Navajo Nation. Research Thrust 1, Materials and techniques for detection of low concentration of pollutants, Research Thrust 2, Next generation energy materials, and Research Thrust 3, Mechanical Properties of Biomaterials.

Title: Scaffolds Mimicking Antigen Presenting Cells
Time Commitment: .60 calendar months
Supporting Agency: DHHS/FDA
Name and address of funding agency's Procuring Contracting/Grants Officer: Kimberly Pendleton
Performance Period: 09/20/18-08/31/21
Level of funding: $1,800,000
Specific Aims: The specific objectives for this project are: (1) Establish SOPs for APC-ms synthesis. This will include identifying MSR critical quality attributes (CQAs) for functional APC-ms and understanding how critical process parameters (CPPs) in MSR synthesis affect those CQAs (2) Develop a process to directly and selectively conjugate surface cues onto lipid bilayers, via click chemistry, to simplify and modularity of APC-ms assembly and function. (3) Characterize residual APC-ms materials during T cell processing, and perform a thorough in vivo safety assessment. The successful achievement of these aims will immediately address key issues related to using APC-ms as an ex vivo T-cell expansion platform.

Title: i3 Center Biomaterials to Promote T Cell Immunity
Time Commitment: 1.92 calendar months
Supporting Agency: National Institutes of Health (NIH/NCI)
Name and address of funding agency's Procuring Contracting/Grants Officer: Amy R Bartosch
Email: amy.bartosch@nih.gov Phone: 240-276-6300
Performance Period: 09/25/19-08/31/24
Level of Funding: $8,192,428

Brief description of project's goals: This i3 Center will create biomaterial-based immunotherapies through marrying the expertise in bioengineering from accomplished investigators at the Wyss Institute with the expertise in cancer immunology, stem cell biology, and clinical oncology from scientists at the Dana-Farber Cancer Institute and Massachusetts General Hospital. We will selectively expand large numbers of highly functional polyclonal antigen-specific CD8 T cells, and explore if adoptive transfer of polyclonal T cells will provide tumor control. Determine if co-delivery of neoantigens and adjuvants with precise nanoscale distribution and stoichiometric loading can boost the development of cytotoxic T lymphocyte anti-cancer responses. Create biomaterials which enable rapid reconstitution of T cells in settings where there are deficiencies in T cell number and repertoire.

Fellowship Support – Dr. Mooney serves as mentor
Title: Anti-Inflammatory Mesenchymal Stem Cell Therapy for Dental Applications (K08DE025292)
Time Commitment: 0 calendar months
Supporting Agency: National Institute of Health (NIH/NIDCR) (PI: Vining, K.)
Name and address of funding agency's Procuring Contracting/Grants Officer: Gabriel Hidalgo
Grants Management Officer, hidalgoge@nidcr.nih.gov Phone: 301-827-4630
Performance Period: 4/1/16-3/31/21
Level of funding: $635,304
Brief description of project's goals: The research goal is to understand how the biophysical properties of the three-dimensional microenvironment influence the ability of mesenchymal stem cells' (MSCs) to modulate immune responses.
Specific Aims: 1, utilize an in vitro model of extracellular matrix stiffness to examine how mechanics affect the anti-inflammatory secretory and transcriptional behavior of adult human bone marrow derived MSCs. 2, investigate the in vitro functional effects of MSCs on human macrophages in co-culture experiments, by measuring the polarization of M1 versus anti-inflammatory M2 macrophages. 3, investigate the in vivo function of MSCs, which are tuned by the stiffness of their microenvironment to increase secretion of anti-inflammatory factors (Aim 1) and promote anti-inflammatory M2 macrophage phenotype (Aim 2). Test the mechanically-tuned human MSCs in vivo by locally injecting MSCs encapsulated in collagen-alginate into an injured rodent dental pulp, and measure the effects on the host inflammatory response.

Title: On-Demand Stem Cell Delivery Systems for Tendon Healing Throughout Aging (F32AG057135)
Time Commitment: 0 calendar months
Supporting Agency: National Institute of Health (NIH/NIA) (PI: Freedman, B.)
Name and address of funding agency's Procuring Contracting/Grants Officer: Jessica Perez, Grants Management Officer, Telephone: 301-403-7739 Email: jessi.perez@nih.gov.
Performance Period: 08/01/17- 07/31/20
Level of funding: $176,598
Brief description of project's goals: Develop and examine a new approach to on-demand TSPC delivery
using implantable biphasic ferrogels.

Specific Aims: 1, Develop and examine the ability of biphasic ferrogels to maintain TSPC behavior prior to release using cells derived from juvenile, adult, and aged tendons. 2, Develop and examine the ability of biphasic ferrogels to deliver TSPCs derived from juvenile, adult, and aged tendons on-demand. 3, Investigate the ability of biphasic ferrogels to restore age-related deficits in tendon homeostasis and healing using a clinically-relevant Achilles tendon rodent model.

Title: Identification of autoantigens using T cell traps (DFS255730)
Time Commitment: 0 calendar months
Supporting Agency: Canadian Institute of Health Research (PI: Zhang, K.)
Name and address of funding agency's Procuring Contracting/Grants Officer: Julie Conrad Program Design and Delivery Manager, Vanier-Banting Programs and CIHR Awards, Canadian Institutes of Health Research, 160 Elgin Street, 10th Floor, Ottawa, ON K1A 0W9.
Performance Period: 09/01/17-08/31/20
Level of funding: $80,483
Brief description of project's goals: Design an injectable biomaterial to improve trapping of autoreactive T cells and to identify their cognate antigens *ex vivo***.**
Specific Aims: 1, Development of an injectable biomaterial to improve autoreactive T cell trapping. 2, Assessing antigen-specificity in injectable T cell traps. 3, Identification of the cognate antigens of autoreactive T cells *ex vivo.*
Title: The role of mechanical stimulation in macrophage-mediated skeletal muscle regeneration in an in vitro injury model (F31AR075367)
Time Commitment: 0 calendar months
Supporting Agency: National Institute of Health (NIH/NIAMS) (PI: McNamara, S.)
Name and address of funding agency's Procuring Contracting/Grants Officer: Yen Thach, Grants Management Officer, 9000 Rockville Pike, Bethesda, Maryland.
Performance Period:06/01/19-05/31/23
Level of funding: $105,889
Brief description of project's goals: Develop an in vitro model of injured skeletal muscle containing myofibers and MPCs and introduce polarized macrophages into this system. I will design and fabricate a cyclic tensile loading device and use this system to explore the effects of cyclic tensile loading parameters, such as strain and frequency, on macrophage modulation of myofiber regeneration and functional repair of the injured skeletal muscle constructs.
Specific Aims: 1, Develop a device to apply cyclic tensile loading to a tissue engineered three-dimensional in vitro model of injured skeletal muscle containing muscle progenitor cells. 2, Incorporate macrophages and explore their influence on muscle regeneration after severe injury under conditions of cyclic tensile loading.
3, Investigate the effects of cyclic tensile loading on signaling mechanisms between macrophages and muscle progenitor cells during regeneration.

PREVIOUS

Title: A New Platform for Burn Treatment and for Delayed Evacuation of Service Members (W81XWH-16-1-0784)
Time Commitment: 0 calendar month

Supporting Agency: DOD (Sub from Eriksson/BWH)
Name and address of funding agency's Procuring Contracting/Grants Officer: Grants Mgmt.
Specialist/Grants Officer, Assistance Agreements Branch 1, U.S. Army Medical Research Acquisition
Activity, 820 Chandler Street, Fort Detrick, MD 21072
Performance Period: 09/30/16-09/29/19
Level of Funding: $274,615
Brief description of project's goals: Develop a new device capable of providing high, local concentrations of antibiotics to severe burns, in order to prevent and eliminate infections. *Subcontractor to the Metis Foundation.*

Title: Prolonged Field Care with Platform Wound Device
Time Commitment: n/a, completed
Supporting Agency: DOD/ (Eriksson/Applied Tissue Technologies, Inc.)
Name and address of funding agency's Procuring Contracting/Grants Officer: Grants Mgmt.
Specialist/Grants Officer, Assistance Agreements Branch 1, U.S. Army Medical Research Acquisition
Activity, 820 Chandler Street, Fort Detrick, MD 21072
Performance Period: 1/1/17-9/6/18 (early termination of subcontract in process)
Level of Funding: $175,000 Total Cost
Brief description of project's goals: Dr. Mooney will develop antibiotic/hydrogel formulations designed to deliver topical antimicrobials to severe blast/burn wounds. He will test these formulations in vitro, and will provide precise descriptions of the antibiotic/hydrogel formulations to Applied Tissue Technologies.

Title: Role of Macrophages in Impaired Wound Healing in Diabetes (1DP3DK108224-01)
Time Commitment: n/a, completed
Supporting Agency: National Institute of Health (NIH/NIDDK)
Name and address of funding Agency's Procuring Contracting/grants Officer: Theresa Jones, M.D.,
Division Diabetes Endocrinology, and Metabolic Diseases, 6707 Democracy Blvd., Bethesda, MD
20892-4878
Performance Period: 09/30/15-08/31/18
Level of Funding: $653,000
Brief description of project's goals: The aim of this proposal is to develop and test the ability of biomaterials capable of localized, sequential release of factors to first recruit macrophages, and then direct these cells to enhance healing in both *in vitro* engineered skin models and in diabetic, neuropathic rodent wounds. *Subcontractor to Beth Israel Deaconess Medical Center.*

Title: Infection Mimicking Biomaterials for Vaccination against Gonadotropin Releasing Hormone
(GnRH)

Time Commitment: n/a, completed
Supporting Agency: Found Animals Foundation
Name and address of funding Agency's Procuring Contracting/grants Officer: Becky Cyr, Program
Manager Michelson Prize and Grants, Found Animals Foundation, Post Office Box 66370, Los Angeles,
CA 90066.
Performance Period: 11/21/14-11/20/17
Level of Funding: $731,567
Brief description of project's goals: The aim of this proposal is to develop a biomaterial-based vaccine against GnRH that can be injected via needle and syringe.

Title: Engineering skeletal muscle with biodegradable hydrogels (5R01DE013349-14)
Time Commitment: n/a, completed
Supporting Agency: National Institute of Health (NIH/NIDCR)
Name and address of funding Agency's Procuring Contracting/grants Officer: Nadya Lumelsky,
PhD., Director of Tissue Engineering and Regenerative Research Programs, Room 618, 6701 Democracy
Blvd, Bethesda, MD, 20892-4878
Performance Period: 07/01/12-06/30/18
Level of Funding: $2,879,184
Brief description of project's goals: The aims of this proposal are to engineer skeletal muscle by developing biodegradable hydrogels, which mediate transplanted cell population of damaged muscle, in concert with delivery of growth factors that mediate revascularization and reinnervation of the damaged muscle.

Title: Stimuli Responsive, Reloadable, Drug Eluting, Smart Hydrogels for Graft Targeted Immunosuppression in Vascularized Composite Allotransplantation (MR141089)
Time Commitment: n/a, completed
Supporting Agency: DoD (subcontract from University of Pittsburg, PI: Gorantla, V.)
Name and address of funding Agency's Procuring Contracting/grants Officer: Elena Howell, Grants
Mgmt. Specialist/Grants Officer, Assistance Agreements Branch 1, U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21072
Performance Period: 07/1/15-06/30/17
Level of Funding: $320,000
Brief description of project's goals: The aim of this proposal is to develop targeted release of embedded anti-rejection therapies (TREAT) technology that will allow for predictable and reliable loco-regional immunosuppression in grafts without systemic toxicity.

Title: Biomaterial-based breast cancer vaccine (5R01EB015498-01A1)
Time Commitment: n/a, completed
Supporting Agency: National Institute of Health (NIH/NIBIB)
Name and address of funding Agency's Procuring Contracting/grants Officer: Dr. Jessica Tucker,

Division of Discovery Science and Technology, Bldg. 2 DEM, Room 200, 6707 Democracy Blvd.,
Bethesda, MD 20892-4878
Performance Period: 04/01/13-09/30/17 (NCE)
Level of Funding: $1,498,939
Brief description of project's goals: The aim of this proposal is to create a new approach to breast cancer vaccines, in which biomaterials that can be introduced into the body in a minimally invasive manner are used to program, in situ, host dendritic cells to generate a potent immune response.

Title: Human anti-MICA monoclonal antibodies for melanoma immunotherapy (MRA 269516)
Time Commitment: n/a, completed
Supporting Agency: Melanoma Research Alliance (Subcontract from DFCI, PI: Wucherpfennig, K.)
Name and address of funding Agency's Procuring Contracting/grants Officer: Louise M. Perkins,
Ph.D., The Melanoma Research Alliance Foundation, 1101 New York Avenue, NW, Suite #620, Washington, DC 20005
Performance Period: 05/01/15-04/30/17
Level of Funding: $100,000
Brief description of project's goals: The aim of this project is to develop antibody responses to modulate tumor tolerance mechanisms.

Title: iPSC-derived repair-responsive fibroblasts to heal diabetic foot ulcers (5R01DK098055)
Time Commitment: n/a, completed
Supporting Agency: National Institute of Health (NIH/NIDDK) (Sub from BIDMC, PI: Garlick, J.)
Name and address of funding Agency's Procuring Contracting/grants Officer: Theresa Jones, M.D.,
Division Diabetes, Endocrinology, and Metabolic Diseases, 6707 Democracy Blvd., Bethesda, MD
20892-4878
Performance Period: 08/01/12-1/31/17
Level of Funding: $321,940
Brief description of project's goals: The aim of this proposal is to differentiate and characterize fibroblast cell lines from iPSC reprogrammed from diabetic foot ulcers to fibroblasts laboratory. 2. Develop polymeric delivery vehicles for the cell transplantation studies in the mouse and rabbit models.

Title: Building the hematopoietic stem cell niche (5R01EB14703-04)
Time Commitment: n/a, completed
Supporting Agency: National Institute of Health (NIH/NIBIB)
Name and address of funding Agency's Procuring Contracting/grants Officer: Rosemary Hunziker,
PhD., Division of Discovery Science and Technology, Bldg. 2 DEM Room 235, 6707 Democracy Blvd,

Bethesda, MD 20892-4878
Performance Period: 09/15/11-07/30/16
Level of Funding: $3,069,914
Brief description of project's goals: The aim of this proposal is creating 3D model of hematopoiesis, in which mesenchymal stem cells (MSCs) and other cells of the osteoblast lineage, and vascular cells have been hypothesized to play a key role in the hematopoietic stem cell (HSC) niche.

Fellowship Support – Dr. Mooney serves as mentor

Title: Designing a synthetic bone marrow niche to overcome immunodeficiency
Time Commitment: 0 calendar months
Supporting Agency: Cancer Research Institute (PI: Shah, N.)
Name and address of funding agency's Procuring Contracting/Grants Officer:
Performance Period: 01/01/17-08/31/18
Level of funding: $0
Brief description of project's goals: In contrast to endogenous bone marrow, proposed to engineer an ectopic bone marrow niche. Composed of 'address labels' to specify T-cell lymphopoiesis in which a synthetic, programmable recapitulation of the bone marrow HSC niche could be used to replenish T-cells of the adaptive immune system by driving the lymphoid lineage program in HSCs in vivo.
Specific Aims: 1, Recapitulate the bone marrow microenvironment to specify lymphopoiesis: A porous injectable scaffold will be combined with signals specifying (i) the formation of an ectopic bone marrow nodule and (ii) lymphocyte commitment of HSCs via a Notch ligand. The presentation of Notch ligands and cytokines will be optimized for lymphocyte generation using in vitro differentiation assays. In vivo, the system will be tested for HSC chemotaxis and colonization.
2, Drive broad and subset-specific lymphocyte reconstitution after HSCT: The ectopic bone marrow will provide additional sites for donor HSCs to engraft, and specify their differentiation into immune cells. The hydrogel will be used to expand the T-and B- cell repertoire by driving the reconstitution of na'ive lymphocytes. The thymic output of T-cells will be quantified and the TCR will be sequenced to assess diversity. (ii) The formation of regulatory T-cells will be specified. 3, Couple immune reconstitution for antigen-specific immunity: The formation of antigen-specific $CD8^+$ cytotoxic T-cells are key in conferring protective immunity after a HSCT. Initially, the robustness of immune reconstitution will be tested by vaccinating mice against model antigen ovalbumin and measuring the antigen-specific T-cell response. Clinically relevant AML targets will be explored. The bone marrow forming hydrogel will be combined with vaccination strategies for preventing the relapse of leukemia after a primary HSCT.

PENDING

Title: Novel Mast Cell Stabilizers for the Management of the Diabetic Foot Ulceration
Time Commitment: .01 calendar months
Supporting Agency: NIH (subcontractor to BIDMC, PI: Veves, A.)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period: 12/1/19-11/30/24
Level of Funding: $142,472
Brief description of project's goals: The goal of our part of the project will incorporate protective hydrogels that allow for a sustained release to the underlying epidermis and dermis. We have previously demonstrated that degradable, injectable alginate gels can provide sustained SP delivery. In this project, we will instead develop bandage-like hydrogels fabricated from alginate to deliver SP.

Title: In situ cell programming scaffolds for potentiating CAR-T cell therapies
Time Commitment: .01 calendar months
Supporting Agency: National Science Foundation (STTR)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period: 01/01/20-12/31/20
Level of Funding: $135,000
Brief description of project's goals: The overall goal of this project is to develop an injectable biomaterial scaffold that amplifies the activity of CAR-T cell therapy by augmenting CAR-T cell number, persistence, and function directly. The Mooney laboratory will perform research that builds off a biomimetic scaffold platform termed Antigen-Presenting Cell-mimetic scaffold (APC-ms) which we have previously described for ex vivo T cell activation.

Title: Fabricating DNA origami with optimal CpG spatial distribution and neoantigens to generate a personalized cancer vaccine towards Th1 polarized immune response.
Time Commitment: .50 calendar months
Supporting Agency: Department of Defense (subcontractor to DFCI, PI: Shih, W.)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period: 02/01/20-01/31/23
Level of Funding: $622,644
Brief description of project's goals: The Mooney lab will aid in design and analysis of in vitro immune cell assays characterizing various agents to be fabricated in the overall studies, and will lead in vivo studies examining the efficacy of the agents in generating immune responses, and providing therapeutic benefit in the relevant tumor models.

Title: Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center: Advancing Dental, Oral, and Craniofacial Regeneration to Clinical Trial Initiation (Competing renewal of U24DE026915)
Time Commitment: 1.2 calendar months
Supporting Agency: National Institutes of Health (NIH/NIDCR)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period:04/01/20-03/31/25
Level of Funding: $2,120,625
Brief description of project's goals: Develop reliable and affordable therapeutic strategies for treating dental diseases.

Title: Polymeric Matrices with defined cell adhesion (Competing renewal of DE013033)
Time Commitment: 1.0 calendar months
Supporting Agency: National Institute of Health (NIH/NIDCR)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period: 04/01/20-03/31/25
Level of Funding: $2,748,899
Brief description of project's goals: The aim of this proposal is to develop materials to enable the regeneration of bony tissues for reconstructive dental and craniofacial applications.
Specific Aims:

Fellowship Support – Dr. Mooney serves as mentor

Title: Impact of the post-ischemia microenvironment in cardiomyocyte plasticity, reprogramming and
Regeneration
Time Commitment: 0 calendar months
Supporting Agency: American Heart Association (PI: de Lazaro del Rey, I.)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period: 01/01/20-12/31/2
Level of funding: $139, 336
Brief description of project's goals:
The overall goal of this proposal is to test if partial reprogramming of CMs into proliferating progenitors can be achieved, that ultimately provides *de novo* CMs to regenerate the tissue and restore heart function after MI.
Specific Aims: 1. Determine whether reprogramming of adult mouse CMs by overexpression of OKSM factors is enhanced or enabled at specific time windows after MI. 2. Determine the role of the IL-6/STAT3 signaling pathway, and of immune and senescent cells, in modulating OKSM CM reprogramming after MI. 3. Investigate if partially reprogrammed CMs re-differentiate into mature counterparts that regenerate a functional myocardium after MI.

Title: Extracellular matrix viscoplasticity as a driver of wound healing in PreTerm Premature Rupture of Membrane (PA-19-130)
Time Commitment: 0 calendar months
Supporting Agency: National Institute of Health (NIH/ NICHD) (PI: Grolman, J.)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period: 04/01/20- 03/31/25
Level of funding: $941,579
Brief description of project's goals: This work investigates how the mechanical properties of the fetal membrane change and become more susceptible to rupture, and how novel stem cell and immunotherapy can address and possibly prevent rupture of the fetal membrane.
Specific Aims: 1, Investigate differences in the mechanical properties of fetal membranes that make them more
susceptible to rupture, as well as the matrix properties that drive the release of polarization and recruitment factors from MSCs. 2, we will investigate how the viscoplasticity of the hydrogels affects MSC phenotype, the time scale mechanotransduction priming occurs, and if the plasticity

of the matrix changes *in situ*. **3**, we develop a therapeutic strategy to address fetal membrane rupture based on the findings from **Specific Aims 1 and 2** by injecting MSC-laden hydrogels with optimal macrophage recruiting and polarizing efficiency into C57BL/6 mice with model pPROM punctures.

Title: Multifunctional tough adhesive hydrogels to recruit, expand, and deliver tendon cells during aging and injury (K99 AG065495)
Time Commitment: 0 calendar months
Supporting Agency: National Institute of Health (NIH/NIA) (PI: Freedman, B.)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period:07/01/20-06/30/25
Level of funding: $934,915
Brief description of project's goals: This study aims to develop and examine a new approach to on-demand tendon cell recruitment, expansion, and release during aging using implantable multifunctional tough adhesive (mTA) fiber composite hydrogels.
Specific Aims: 1, develop and examine the ability of tough hydrogels containing chemotactic agents to recruit tendon-derived cells, promote their proliferation, and increase expression of tendon markers throughout aging and injury *in vitro* and *in vivo;* 2, develop and examine the ability of hydrogel degradation and embedded fibers to template mature tendon, drive expression of tendon markers, and promote cell release from the scaffold to the injury site throughout aging and injury, *in vitro* and *in vivo*; and 3, investigate the ability of the tough adhesive hydrogel system to restore age-related deficits in tendon homeostasis and healing using a clinically-relevant Achilles tendon rodent model.
Specific Aims: 1, *(K99 Phase)* develop and examine the ability of tough hydrogels containing chemotactic agents to recruit tendon-derived cells, promote their proliferation, and increase expression of tendon markers throughout aging and injury, *in vitro* and *in vivo*. 2, *(K99□R00 Phase)* develop and examine the ability of hydrogel degradation and embedded fibers to template mature tendon, drive expression of tendon markers, and promote cell release from the scaffold to the injury site throughout aging and injury, *in vitro* and *in vivo.* 3, *(R00 Phase)* investigate the ability of the tough adhesive hydrogel system to restore age-related deficits in tendon homeostasis and healing using a clinically relevant Achilles tendon rodent model *(sample size details in Vertebrate Animals).*

Title: Organotypic modeling of immunoregulation in obesity using stem cell-derived human adipose tissue
Time Commitment: 0 calendar months
Supporting Agency: National Institute of Health (NIH/NIDDK) (PI: Khalil, A. MENTOR: Mooney, D.J.)
Name and address of funding agency's Procuring Contracting/Grants Officer: pending
Performance Period:07/01/20-06/30/22
Level of funding: $125, 356
Brief description of project's goals: Use human pluripotent stem cell technology to model adipose tissue immunoregulation in obesity- and type 2 diabetes-mimicking culture conditions to test the hypothesis that loss of Treg-mediated immunoregulation within human adipose tissue

results in a permanent shift in resident macrophage populations and production of inflammatory cytokines, driving impaired adipocyte function.
Specific Aims: 1, Derive relevant cell types needed to study adipose tissue immunoregulation from hPSCs and create a vascularized organotypic model of hAT. 2, Optimize obesity- and T2D-mimicking cultures for organotypic hAT. 3, Utilize modeling to quantify how Mφ phenotype influences hAT phenotype and function, as well as how Tregs regulate Mφ phenotype in hAT. I will incorporate hPSC-derived Tregs and Mφ into the organotypic hAT and compare changes in adipocyte phenotype and function in high glucose and free fatty acid cultures. I will use statistical modeling to quantitatively describe how inflammatory and anti-inflammatory Mφ phenotypes influence adipocyte phenotype and function, and how Tregs regulate Mφ phenotype within hAT in obesity- and T2D-mimicking culture conditions.

Other Support, Simon Talbot

Current

Title:	*A novel approach to lower extremity amputation to augment volitional motor control and restore proprioception*
Time Commitment:	6.5% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871
Performance Period:	7/1/2017-6/30/2021
Level of funding:	$2,383,103
Project's Goals:	The goal of this project is to develop and validate a new surgical technique to lower extremity amputation that incorporates agonist-antagonist myoneural interfaces
Specific aims:	1. To define a standardized approach to the performance of a novel operative procedure for both below knee (BKA) and above knee (AKA) amputations. 2. To measure the degree of volitional motor activation and excursion achievable in the residual limb constructs, and to determine the optimal configuration and design of such constructs. 3. To describe the extent of proprioceptive and other sensory feedback achievable through the employment of these modified surgical techniques. 4. To validate the functional and somatosensory superiority of the proposed amputation technique over standard approaches to BKA and AKA. 5. To develop a modified acute postoperative rehabilitation strategy suited to this new surgical approach.
Overlap:	None

Title:	*A novel approach to upper extremity amputation to augment volitional motor control and restore proprioception*
Time Commitment:	2% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871
Performance Period:	9/30/2018-9/29/2021
Level of funding:	$3,000,000
Project's Goals:	The goal of this project is to develop and validate a new surgical technique to upper extremity amputation that incorporates agonist-antagonist myoneural interfaces
Specific aims:	1. To define a standardized approach to the performance of a novel operative procedure for both below elbow (BEA) and above elbow amputations (AEA). 2. To measure the degree of volitional motor activation and excursion achievable in the residual limb constructs, and to determine the optimal configuration and design of such constructs. 3. To describe the extent of proprioceptive feedback achievable through the employment of these modified surgical techniques. 4. To validate the

	functional and somatosensory superiority of the proposed amputation technique over standard approaches to BEA and AEA. 5. To develop a modified acute postoperative rehabilitation strategy suited to this new surgical approach.
Overlap:	None
Title	*Psychosocial predictors of VCA outcomes*
Time Commitment	12.5% effort (PI)
Supporting Agency	US Department of Defense
Grants Officer	Sandra Rosario, USAMRAA, 843 Chandler St, Fort Detrick, MD 21740, (301) 619-4063
Performance Period	07/1/2017-06/30/2020
Level of funding	$563,380
Project's Goals	The goal of this project is to determine key factors in determining outcomes for VCA patients.
Specific aims	1. To evaluate prospectively collected data on the International Registry of Hand and Composite Tissue Transplantation (demographics, medical/surgical factors) to determine variables associated with transplant 'success.' 2. To develop a model based on expert opinion, focusing on psychosocial parameters, to help objectify the psychosocial evaluations of hand transplant patients. 3. To validate the model developed in Aims 1 and 2 in actual patients from the several large volume centers where complete data is available.
Overlap	None
Title:	*Extremity regeneration of soft tissue injury using growth factor-impregnated gels (W81XWH-16-2-0067)*
Time Commitment:	10% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871
Performance Period:	09/30/2016-09/29/2020
Level of funding:	$2,100,000
Project's Goals:	The goal of this project is to investigate the use of growth-factor impregnated hydrogels for the improvement of nerve regeneration and limb function.
Specific aims:	1. Tto determine if the use of injectable hydrogel combined VEGF and IGF-1 can improve nerve growth in a large animal model, and thereafter to determine dose, scheduling, and produce a product for FDA approval.
Overlap:	None
Title:	*T-cells and rejection in vascularized composite allotransplants*
Time Commitment:	6.5% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871

Performance Period:	9/30/2018-9/29/2021
Level of funding:	$263,200
Project's Goals:	The goal of this project is to determine the relative contribution of donor versus recipient-derived T cells in VCA rejection, elucidate if monitoring pathogenic T cell clones in the circulation can be used as a rejection biomarker, and establish the correlation of rejection in sentinel flaps and clinical VCA allografts to determine the clinical utility of sentinel flaps as remote site rejection biomarkers.
Specific aims:	1. Determine the role of donor versus recipient T cells in VCA rejection. 2. Elucidate if monitoring pathogenic T cell clones in the circulation can be used as a rejection biomarker. 3. Establish the correlation of rejection in sentinel flaps and VCA allografts.
Overlap:	None
Title:	*A novel approach to lower extremity residual limb revision to augment volitional motor control, restore proprioception and reverse limb atrophy*
Time Commitment:	0.1% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871
Performance Period:	9/30/2019-9/29/2022
Level of funding:	$3,000,000
Project's Goals:	The hypothesis of this research protocol is that we will be able to modify the residual limbs of patients who have already undergone lower extremity amputations so as to include biological actuators that will enable the successful employment of next generation lower extremity prostheses, diminish/eliminate phantom limb pain, restore proprioception and regenerate lost muscle mass.
Specific aims:	1. To develop a standardized operative technique for both above knee (AK) and below knee (BK) amputation revision procedures that includes AMIs to restore musculotendinous proprioceptive capabilities. 2. To assess the capacity for these actuators to provide enhanced motor control and sensory feedback, as well as ablate phantom limb symptomatology and augment residual limb muscle mass. 3. To determine the reinnervation time course and longevity of these biological constructs. 4. To validate the functional and somatosensory superiority of the proposed revision technique over standard approaches to BKA and AKA. 5. To develop a modified acute postoperative rehabilitation strategy suited to this new surgical approach.
Overlap:	None

Previous

Title:	*Engineering skeletal muscle with biodegradable hydrogels (4R01DE013349- 16)*
Time Commitment:	5% effort

Supporting Agency:	National Institutes of Health
Grants Officer:	Gabriel Hidalgo, NIDCR, 6705 Rockledge Drive, Bethesda, MD 20892-7986
Performance Period:	08/28/2014-06/30/2017
Level of funding:	$91,629
Project's Goals:	The goal of this project is to test and further refine the use of biodegradable hydrogels in ischemia tissue and denervated tissue to improve tissue viability and recovery.
Specific aims:	1. To examine the ability of alginate gel-based delivery of VEGF and IGF-1 to enhance engraftment and function of a denervated tibialis anterior muscle, in young and aged mice and in a rabbit gracilis muscle transfer model.
Overlap:	None

Title:	*Design and testing of a robotic system to perform microscale anastomosis (URAD)*
Time Commitment:	5% effort
Supporting Agency:	The Charles Stark Draper Laboratory
Grants Officer:	Mary Luther, Draper Laboratory, 555 Technology Square, Cambridge, MA 02139-3563, (617) 258-2361
Performance Period:	7/1/2013-6/30/2014
Level of funding:	$110, 000
Project's Goals:	The project goals were to develop micro-robotic technology for microsurgery.
Specific aims:	1. To miniaturize and improve fidelity of micro-instruments through the development of micro-sensors and to modify existing robotic control systems for this purpose.
Overlap:	None

Title:	*A novel protocol for upper extremity restoration by transplantation with intent for tolerance induction (W81XWH-12-2-0037)*
Time Commitment:	5% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871
Performance Period:	9/30/2012-9/29/2017
Level of funding:	$ 2,005,315
Project's Goals:	The goal of this project is to induce tolerance to upper extremity allografts in four human transplant recipients through a mixed chimerism approach.
Specific aims:	1. To perform upper extremity transplantation followed two months later by delayed bone marrow transplantation in four subjects. 2. To determine whether mixed lymphohematopoietic chimerism reduces the immune response to upper extremity allografts by in vitro analysis of recipient T-cell subtypes and function, allowing for reduction or withdrawal of immunosuppression after upper extremity/bone marrow transplantation. 3. To study the outcomes of upper extremity allotransplantation in a cohort

	of four patients for a period of one year post-transplant.
Overlap:	None

Pending

Title:	*Use of the Patient Generated Index (PGI) for evaluating patient experience in amputation and reconstruction*
Time Commitment:	25% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871
Performance Period:	7/1/2020-6/30/2023
Level of funding:	$1,500,000
Project's Goals:	The goal of this project is to use the PGI to better document and longitudinally track patient experience after amputation and treatment
Specific aims:	1. Protocolize the Patient Generated Index (PGI) in an online platform for ease of administration. 2. Obtain PGI data from a wide range of upper extremity amputees, to inform baseline characteristics. 3. Obtain a subset of longitudinal PGI data from upper extremity prosthetic and transplant patients, focusing on changes over time.
Overlap:	None

Title:	*Core Outcomes in Vascularized Composite Tissue Allotransplantation (VCA) and Extremity Reconstruction (COVER)*
Time Commitment:	25% effort
Supporting Agency:	US Department of Defense
Grants Officer:	Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871
Performance Period:	7/1/2020-6/30/2023
Level of funding:	$1,500,000
Project's Goals:	The goal of this project is to undertake a comprehensive review and qualitative analysis to better inform outcome measures for upper extremity amputees
Specific aims:	1. Conduct a comprehensive systematic review of quality of life and functional measures of upper extremity amputees. 2. To conduct focus groups with nominal group technique, and an international Delphi survey to establish consensus on critically important outcomes for upper extremity amputees. 3. To conduct multi-stakeholder consensus workshops to establish core outcomes in VCA and extremity reconstruction.
Overlap:	None

CURRENT / PENDING SUPPORT

NAME	POSITION TITLE
COL Leon J. Nesti, MD, PhD	Chief, Clinical and Experimental Orthopaedics, WRNMMC

CURRENT SUPPORT:

Title: Establishment of Peripheral Nerve Injury Data Repository to Monitor and Support Population Health Decisions
Funding Agency: MSIS/JPC-1
Project Goal: We propose to carry out epidemiologic chart reviews of approximately 400 patients with combat related peripheral nerve injuries who were referred to WRNMMC or SAMMC for tertiary care. A data registry will be established and algorithms developed to support health decisions.
Specific Aims/Tasks: Specific Aim 1. Establish a database registry of CR-PNI mechanisms, management and outcomes using both retrospective chart review and prospective patient enrollment. Specific Aim 2. Develop algorithms based upon evaluation of the CR-PNI registry to establish correlations between clinical history, management and outcomes in order to provide recommendations for clinical care that will improve outcome for peripheral nerve injury patients.
Performance Period: 10/1/2016 – 5/31/2020
Level of Funding: $851,000
Time Commitment: 10%

Title: Clinical Evaluation of Decellularized Nerve Allograft with Autologous Bone Marrow Stem Cells to Improve Peripheral Nerve Repair and Functional Outcomes
Funding Agency: CDMRP
Project Goal: The proposed project is to conduct a phase I clinical safety evaluation of the synergistic effect of co treatments of a commercially available decellularized processed peripheral nerve allograft scaffold (Avance® Nerve Graft, AxoGen, Alachua FL) combined with autologous bone marrow stem cells (BMSC) for the reconstruction of mixed peripheral nerve gaps between 3 and 7 cm in length
Specific Aims/Tasks: Specific Aim 1 / Primary Outcome: Assess the safety profile of the processed nerve allograft when combined with autologous BMSC's as a treatment for reconstruction of mixed peripheral nerve gaps up to 70 mm. Specific Aim 2 / Secondary Outcome: Measure the efficacy of the processed nerve allograft when seeded with BMSC's and compare the outcomes to historical autograft and Avance® values by comparing the level of functional recovery. As well as compare other secondary efficacy endpoints such as: time to recovery, recovery to baseline, level and rate of reinnervation, quality of life, economic data and correlation of short- and long-term outcomes with regard to MESS and LSI scores
Performance Period: 07/01/2015 – 06/30/2020
Level of Funding: $2,325,412
Time Commitment: 10% effort

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

Title: Novel anti-fibrotic strategies in the targeted treatment and prevention of post-traumatic Heterotopic Ossification and enhancement of post-traumatic tissue regeneration.
Funding Agency: CDMRP
Project Goal: The proposed project is to research in-vitro and test in a small animal model a combination of Rapamycin and Proleukin as a novel treatment strategy to prevent the development of post-traumatic heterotopic ossification, reduce tissue fibrosis and promote normal tissue regeneration
Specific Aims/Tasks: Specific Aim 1: To determine the effectiveness of Rapamycin treatment in preventing fibrosis of muscle-derived MPCs in a cell culture system. Specific Aim 2: To assess the efficacy of Rapamycin-based therapy in preventing fibrosis and ectopic bone formation in an animal model. Specific Aim 3: Evaluate co-treatment with the immune modulator Proleukin to reduce an anticipated immunosuppression side effect of primary treatment.
Performance Period: 10/1/2016 – 9/30/2020
Level of Funding: $499,664
Time Commitment: 5%
Name and Address of Funding Agency's Procuring Contracting/Grants Officer:
Jason Kuhns, U.S. Army Medical Research Acquisition Activity Contracting Officer
843 Chandler Street, Fort Detrick, MD 21740
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Title: Phase 2 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Use as a Vascular Prosthesis for Femoro-Popliteal Bypass in Patients with Peripheral Arterial Disease
Funding Agency: USAMMDA
Project Goal: Evaluate the safety and tolerability of the Humacyte HAV in PAD patients undergoing femoro-popliteal bypass surgery and determine the patency rate of the Humacyte HAV.
Specific Aims/Tasks: Task 1: Primary objectives are to evaluate the safety and Tolerability of the Humacyte HAV in PAD patients.
Task 2: Secondary objectives are to assess changes in the PRA response after HAV implantation to determine mechanical stability of the HAV based on freedom from aneurysmal degeneration on duplex ultrasound and CT imaging.
Task 3: Endpoints will be assessed over a period of up to 60 months after HAV implantation.
Performance Period: 9/1/2019 – 8/31/2022
Level of Funding: $320,247

Time Commitment: 5% effort
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer

PREVIOUS SUPPORT:

Title: Early Identification of Molecular Predictors of Heterotopic Ossification following Extremity Blast Injury: Animal Model Correlation with Human Disease
Funding Agency: CDMRP
Project Goal: The goal of this project is to explore the hypothesis is that the biologic processes that characterize heterotopic ossification in a blast amputation model in the Sprague-Dawley rat will closely resemble those observed in battle-injured soldiers. Correlation of animal and human HO findings will allow identification of common biomarkers that are present early in the process and are predictive of HO formation in wounded soldiers at greatest risk. These high-risk individuals would ultimately be enrolled in a clinical trial of therapeutic interventions known to effectively prevent HO in the civilian setting.
Specific Aims/Tasks: (1) To correlate gene- and protein- level expression related to osteogenesis in the animal model and human tissue. (2) To identify early-appearing gene- and protein-level expression in the animal model that predicts eventual development of human HO. (3) To validate early-appearing biomarkers to predict development of HO
Performance Period: 09/30/2013 – 12/30/2017
Level of Funding: $434,497
Time Commitment: 10% effort
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:
Lisa Sawyer, U.S. Army Medical Research Acquisition Activity
820 Chandler Street, Fort Detrick, MD 21740-5014
Lisa.sawyer22.civ@mail.mil

Title: Development and Characterization of in vivo Models of Explosive Blast-Related Spinal Column Injury
Funding Agency: DMRDP
Project Goal: To determine the influence of blast exposure on invertebral disc's and muscle's molecular profile (gene expression on RNA level) on rat model.
Specific Aims/Tasks: Real-time PCR results (gene expression on transcription level) in blast and control rats IVD's and muscle at various time points.
Performance Period: 06/13/2014 – 04/30/2016
Level of Funding: $396,800
Time Commitment: 10% effort
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:
Steven Beck, USUHS
4301 Jones Bridge Road, Bethesda MD 20814
301-295-3970
Steven.beck@usuhs.edu

Title: Stem Cell-Based Neurotrophic Enhancements of an Aligned Nanofiber Scaffold for Nerve Repair
Funding Agency: USAMRAA
Project Goal: To validate the efficacy of the MPC scaffold composite device in vivo using a rabbit model of nerve injury.
Specific Aims/Tasks: 1) To verify nanofibers alignment to the longitudinal axis of the device and determine the correlation between device density and distance between aligned fibers and to optimize the fabrication parameters for this device by determining range of fiber densities that will yield sufficient tensile and suture retention strengths that are necessary for surgical handling. 2) To determine whether the devices from Specific Aim 1 allow sufficient space between the aligned fibers for the migration of traumatized muscle-derived MPCs and microvascular endothelial cells through the device. 3) To verify that the axon scaffolding devices will support the neurotrophic functions of the MPCs and to validate the efficacy of the MPC scaffold composite device using an in vitro nerve regeneration model.
Performance Period: 9/1/2010-3/30/2016
Level of Funding: $313,643
Time Commitment: 10% effort
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:
Abigail Strock, U.S. Army Medical Research Acquisition Activity Grant Specialist - Gold Team
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301-619-2342
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PENDING SUPPORT:

Title: Electrical Stimulation to Accelerate Nerve Regeneration
Funding Agency: USAMRAA
Project Goal:
Specific Aims/Tasks: 1) Aim 1: Evaluate the efficacy of brief electrical stimulation to accelerate nerve regeneration following ulnar nerve decompression in a multi-center prospective, randomized controlled clinical trial (n=64).
Aim 2: Evaluate the efficacy of brief electrical stimulation for nerve regeneration following mixed or
motor nerve transection of the upper extremity repaired with either A) nerve transfer or B) direct nerve
repair or grafting in a multi-center prospective randomized clinical trial (n=44).
Performance Period: 7/1/2020 – 6/30/2023
Level of Funding: $312,599
Time Commitment: 5% effort
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer

Title: Optimization and assessment of a biologic to improve functional recovery after peripheral nerve injury

Funding Agency: NIH/NINDS
Project Goal: Conduct a comprehensive nonclinical assessment of the regenerative potential of the REST
phosphomimetic peptide after peripheral nerve injury.
Performance Period: 9/15/2020 – 8/31/2021
Level of Funding: direct: $125,693.00; Total (direct + indirect): $188,545.04
Time Commitment: 10% effort
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer
Grants Management Branch National Institutes of Neurological Disorders and Stroke 6001 Executive
Boulevard, Suite 3290, MSC 9537 Rockville, MD 20852 (Express Mail) Bethesda, MD 20892-9537 (Regular
Mail)
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