The following have been modified:

U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
AWARD SPECIFIC RESEARCH TERMS AND CONDITIONS
WITH INSTITUTIONS OF HIGHER EDUCATION, HOSPITALS, AND NON-PROFIT
ORGANIZATIONS

DIVISION I – AWARD COVER PAGES

A. Award Information
1. Department of Defense Awarding Office: USAMRAA
2. Award number/Project title: W81XWH2010885 Regenerative Rehabilitation Solutions to Improve
   Functional Limitations and Plasticity Following Volumetric Muscle Loss
3. Type of Award: Grant
4. Type of Award Action: Modification
5. i. Brief description of project or program:

   Technical Abstract
   
   Focus Area: Our proposed work directly addresses the DMRDP JCP-8/CRMRP RESTORE Focus Areas of i) optimization of Warfighter performance following limb trauma or loss, and ii) solutions to accelerate
   recovery and restore Warfighter performance in training and operational environments.

   Background, Objective/Hypothesis: There are currently no short- or long-term guidelines for the
   restoration of tissue function following volumetric muscle loss (VML) injury and concomitant bone
   polytrauma. We believe that evidence-based approaches for VML rehabilitation and regenerative
   rehabilitation are limited by a predominant focus in the field on engineering strategies that neglects the
   physiology of the tissue and overwhelming fails to include clinically relevant outcomes measurements. The
   proposed research represents a substantive departure from this status quo by leveraging our insight into the
   VML pathophysiology in order to correct the dysfunction and resistant plasticity to improve short- and
   long-term physiologically relevant outcome measurements of muscle and bone function. Our central
   hypothesis is that to improve function (i.e., increases in muscle power, strength, oxidative capacity, and
   fatigue resistance) following VML injury i) optimal evidence-based rehabilitation needs to be developed;
   ii) treatment of physiologic limitations needs to occur in conjunction with rehabilitation; and iii) long-term
   impacts of both injury and treatment need to be understood across the neuromusculoskeletal system (e.g.,
   bone) to support long-term health of those injured.

   Research Aims and Strategy for Level 2 Proposal: We previously developed a multi-muscle VML injury
   model to the posterior compartment of the mouse which will be used in this proposal, the injury
   encompasses the gastrocnemius, plantaris, and soleus muscles, and the posterior compartment injury is a
   useful model for chronic evaluations because the muscle group is highly active (with adjacent bone)
   playing a role in normal ambulation and weight bearing for the animals. Our clinically relevant outcome
   measurements will include skeletal muscle power, fatigue resistance, oxidative capacity, joint range of
   motion, and bone ultimate load and morphology (e.g., cross-sectional moment of inertia). These outcomes
   will be evaluated across three specific aims.
   
   Specific Aim 1: Identification of multi-modal rehabilitation parameters to improve lower limb functionality.
   We have validated muscle electrical stimulation, voluntary wheel running, and whole body vibration as
   tools to enhance muscle contractile function, and passive ankle movements as a tool to improve joint range
   of motion following VML injury. We propose a combination approaches that will adjust treatment intensity
   (low/high).
Specific Aim 2: Regenerative rehabilitation solutions to maximize lower limb functionality. Our ongoing work indicates full restorative function with rehabilitation is limited by dysregulated muscle signaling and extensive pathologic fibrotic tissue deposition. We propose a regenerative rehabilitation approach that will utilize technologies we have identified to address the underlying muscle pathophysiology in combination with our validated rehabilitation strategies and any multi-modal strategies identified. Technologies include fibrosis inhibitors, oxidative capacity stimulators, and muscle atrophy suppressors.

Specific Aim 3: Addressing muscle-bone interactions following VML injury. Our strong preliminary data show bone function and quality declines after VML injury, and may be resistant to adaptation. Bones will be collected and analyzed for function and quality as part of the studies in both Aims 1 & 2. However, additional research is required to better understand the unique muscle-bone interaction and challenges with VML. To address this concern, we will evaluate a regenerative rehabilitation approach to address a muscle-bone polytrauma and evaluate a micro-bone defect model combined with 2-photon microscopy that will enable us to identify confounding factors to bone remodeling in the presence of a VML injury.

Impact: Current rehabilitation strategies do little for the recovery of muscle function and may in fact be detrimental, this presents a frustrating clinical problem for the VML injured patient and clinical care team. This work will advance the efficacy of regenerative rehabilitation approaches and can impact a range of military service members from those acutely injured in current and forthcoming conflicts to those that have already transitioned to the VA health care system and are confronting the chronic devastating outcomes of VML injury.

ii. Funding Overview

<table>
<thead>
<tr>
<th></th>
<th>Federal funds</th>
<th>Cost Sharing</th>
<th>Total amount</th>
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<tbody>
<tr>
<td>a. Obligated or deobligated this action</td>
<td>$764,207</td>
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<td>b. Cumulative obligations to date, including this and previous actions</td>
<td>$1,499,649</td>
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<td>$1,499,649</td>
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<td>c. Planned project costs in the currently approved budget through the end of the period of performance, to include any future incremental funding obligations</td>
<td>$1,499,649</td>
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<td>d. Total value, which includes any unexercised options for which amounts were established in the award</td>
<td>$1,499,649</td>
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6. Obligation/Effective Date: See SF-26, Block 20c.
7. Period of performance: 15 September 2020 through 14 September 2024
8. Authorities: This award is made under the authority of 10 U.S.C. 2358.
9. Catalog of Federal Domestic Assistance Number: 12.420-Military Medical Research and Development
10. Project Performance Information:
   i. This award is for research and development. Construction activities under this award are not authorized. (Reference Department of the Army Pamphlet 420-11, dated 18 March 2010, for the definition of construction activities.)
   ii. Statement of Work and Budget: The revised Statement of Work (SOW) dated 27 July 2020 and the revised budget dated 26 August 2020 for your application submitted in response to the Fiscal Year 2019 DoD Department of Defense, Defense Health Program, Congressionally Directed Medical Research Programs (CDMRP), Defense Medical Research and Development Program, Joint Program Committee 8/Clinical and Rehabilitative Medicine Research Program Restoring Warfighters with Neuromusculoskeletal Injuries Research Award (RESTORE) Program Announcement (Funding Opportunity Announcement Number W81XWH-19-DMRDP-CRMRP-RESTORE, which closed 16 December 2019) are incorporated herein by reference. You may rebudget allowable costs in accordance with applicable cost principles and in accordance with the