Congressionally Directed Medical Research Programs

PEER REVIEWED ORTHOPAEDIC RESEARCH PROGRAM

PORTFOLIO SUMMARY

June 20, 2017

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Acronyms

AFS	Amniotic Fluid-Derived Stem Cell
ATLAS	Ambulatory Tibial Load Analysis System
BADER	Bridging Advanced Developments for Exceptional Rehabilitation Consortium
BCT	Biomechanical Computed Tomography
BMP2	Bone Morphogenetic Protein Type 2
CBT	Cognitive Behavioral Therapy
CCCRP	Combat Casualty Care Research Program
CDMRP	Congressionally Directed Medical Research Programs
CMF	Craniomaxillofacial
CPGs	Clinical Practice Guidelines
CRMRP	Clinical and Rehabilitative Medicine Research Program
CT	Computed Tomography
DK	Developmental Knowledge
DoD	Department of Defense
ETD	Electric Terminal Device
FDA	US Food and Drug Administration
FLAG	Force Limiting Auto Grasp
FLOW	Fluid Lavage of Open Wounds
FY	Fiscal Year
HO	Heterotopic Ossification
IAF	Intra-Articular Fracture
ICD	International Classification of Diseases
ICE	Intra-socket Cooling Element
IED	Improvised Explosive Device
IMFW	Identify and Manage Fractures/Wounds
IND	Investigational New Drug/Device

JPC	Joint Program Committee
M	Million
METRC	Major Extremity Trauma Research Consortium
miR	microRNA
MSC	Mesenchymal Stem Cell
MTF	Military Treatment Facility
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OEF	Operation Enduring Freedom
OETRP	Orthopaedic Extremity Trauma Research Program
OIF	Operation Iraqi Freedom
PEG	Polyethylene Glycol
PLUL	Prevent Loss of Use of Limb(s)
PNS	Peripheral Nerve Stimulation
PRO	Patient-Reported Outcome
PRORP	Peer Reviewed Orthopaedic Research Program
ProFit	Prosthetic Fit Assessment in Transtibial Amputees Secondary to Trauma
PTOA	Post-Traumatic Osteoarthritis
RIC	Rehabilitation Institute of Chicago
RTD	Return to Duty
RTW	Return to Work
SAMMC	San Antonio Military Medical Center
TAOS	Transtibial Amputation Outcomes Study
TMR	Targeted Muscle Reinnervation
VA	Department of Veterans Affairs
VST	Virtual Stress Testing

Executive Summary

The Peer Reviewed Orthopaedic Research Program (PRORP), executed by the Congressionally Directed Medical Research Programs (CDMRP), is a congressionally supported research program focused on the improvement of care and recovery of the nation's military personnel who suffer traumatic extremity wounds while in service to their country. The PRORP seeks to develop evidence to support new clinical practice guidelines (CPGs) and new procedures, technologies, and drugs to help reduce the burden of injury for wounded Service members and aid in their recovery and increase return-to-duty (RTD)/return-to-work (RTW) rates.

The goal of this Portfolio Summary is to provide a concise report of the progress made toward improved care and recovery for wounded Service members via PRORP-funded research, as well as a systematic snapshot of the status of investments in the PRORP portfolio since its establishment in fiscal year 2009 (FY09). The report may be of use to the PRORP Programmatic Panel and others in determining existing knowledge and materiel gaps in orthopaedic-relevant fields and deciding how to allocate future funding (if available) from Congress in support of this program. Projects that have produced successful, significant outcomes are listed within this Portfolio Summary, as well as a brief synopsis of the overall project accomplishments.

The PRORP Portfolio Summary is comprised of several chapters to help organize the presented data. The summary begins with an Introduction chapter that highlights the PRORP program history, funding, future plans, and the overall performance of the program. Background information and investments made in each of the five research areas of the PRORP are summarized in Chapter II. The research areas from FY09 through FY15 for the PRORP are organized into the following categories within Chapter II: Tissue Engineering and Repair, Prosthetics and Orthotics, Prevention and Treatment of Complications, Rehabilitation and Biomechanics, and Pain Management and Patient Reported Outcomes. The Consortia chapter (Chapter III) provides an overview of the two major consortia efforts funded by the PRORP: the Major Extremity Trauma and Rehabilitation Consortium (METRC) and the Bridging Advanced Development for Excellent Rehabilitation (BADER) Consortium. Finally, the PRORP Program Outcomes chapter (Chapter IV) provides a brief highlight of publications, patents, and presentations produced by investigators as part of the program.

Though many of the projects are still in progress, the Portfolio Summary is intended to provide an illustration of the eventual impact that these technologies and projects may have on the care of wounded Service members and the general public. The graphs and information presented within the summary are based on data received as of June 20, 2017.

Individuals seeking additional information may submit their request to the CDMRP Public Affairs Office at usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil or 301-619-9783.

I: Introduction

Program History

Advances in protective gear for military Service members have led to an increase in survivability. Many Service members involved in once-fatal incidents have been saved and/or resuscitated with the help of advances in care and materiel products derived from modern research. The increase in survivability and use of modern body protective gear also has resulted in an increase in the number of Service members and Veterans with extremity injuries. Orthopaedic injuries sustained during combat-related activities tend to be very heterogeneous and complex in nature, typically involving multiple tissues, such as skin, bone, muscle, cartilage, and nerves. These injuries are sustained in harsh environments where access to optimal acute care can be limited. In addition, these injuries are also distinct from those seen in a civilian setting since they more frequently involve multiple limb trauma, open fractures, major tissue loss, and a high degree of wound contamination.

The Department of Defense (DoD) PRORP was initiated in 2009 with a $112 million (M) dollar investment from two appropriations acts: $61M from the Consolidated Security, Disaster Assistance, and Continuing Appropriation Act, 2009, and $51M from the Supplemental Appropriations Act, 2009.[1] During appropriations discussions, the House noted that,[2]

> "Serious limb trauma, vascular injury, major limb tissue disruption and blood flow disruption contribute heavily to U.S. military casualties. Amputation following battlefield injury now occurs at twice the rate of past wars. Recent advances in battlefield medical treatments have focused on reducing time from injury to evacuation and treatment, but the consequences of blood flow disruption to damaged limb tissue remains a major cause of permanent disability or death among military war fighters."
>
> "Extremity injuries are the number one battlefield injury. Understanding how to prevent, treat, and rapidly recover from orthopedic injuries should be a top priority for the Military Health System. Further, the Committee believes that dynamic research and treatment is necessary to provide servicemembers the greatest ability to recover from injuries sustained on the battlefield."

While the exact funding amounts were later revised, these statements have served to guide investment and program priorities since the initiation of the PRORP. Instructions from Congress indicated that the scope of research funded by the program would be broad, including topics such as prevention, treatment, rehabilitation, and prosthetics/orthotics. Congress also clarified that a

[1] Congressionally Directed Medical Research Programs Annual Report 2009. http://cdmrp.army.mil/pubs/annreports/2009annrep/2009annreport.pdf.
[2] House Report 110-279, 110th Congress, 1st Session. https://www.gpo.gov/fdsys/pkg/CRPT-110hrpt279/html/CRPT-110hrpt279.htm.

focus on battle-related injuries was envisioned and that non-battle injuries would be included only if they were similar to combat or combat-related injuries.

In May 2009, a stakeholders meeting was held to direct investment of the new program. During that meeting, a diverse group of stakeholders created a list of perceived orthopaedic care gaps, related military injuries, and opportunities for advancement. The program grouped these gaps into areas of acute battle injuries, definitive care of battle injuries, rehabilitation, and prosthetics/ orthotics, and included them in the program's solicitation of research projects. Over the past several years, these areas of focus have been modified and categorized into surgical care and rehabilitation topics. As such, there has been an evolution in the type of research funded and the focus of the program, from more early-stage technologies to manage bone and cartilage damage to more integrated therapies for clinical management of disease.

Between FY09 and FY15, the PRORP funded 218 projects, including three large consortia awards. The consortia efforts are designed to bring military patients, leading researchers, and military treatment facility (MTF) clinicians together with the infrastructure, patients, and expertise of highly qualified civilian organizations to form partnerships that will ultimately provide new solutions along the continuum of care for wounded Service members with orthopaedic injuries. These consortia supplement the individual awards in the portfolio and are designed to enable the execution of large clinical trials for both surgery- and rehabilitation-related trauma topics.

Future Plans

In keeping with the congressional intent of the PRORP, the program will continue its commitment to support military-relevant orthopaedic trauma research to benefit Service members, Veterans, and the general public. The program has supported, and will continue to support, research projects in several topic areas that have or will produce tangible products, improvements in surgical care techniques, updates in CPGs, and other knowledge products to help return orthopaedically injured persons to work, to play, and to duty.

As PRORP moves into its ninth year, the focus on addressing the current and future needs of Service members and Veterans will be strengthened. The approach by which the program finds and funds innovative and impactful research in the coming years also will be more systematic. The PRORP will consider potential threats to our nation and military in order to determine our current medical capabilities and their corresponding gaps. The program will work with other DoD and federal organizations, as well as non-federal agencies, to ensure that we are working together to close these capability gaps. By the end of 2018, the PRORP will have compiled a 5-year strategic investment plan that will detail how the program will fund research in order to fill current and future medical needs. The plan also will detail how the PRORP intends to support and encourage new ideas, rigorous research, and product-driven projects that will bring concrete solutions to our nation's Service members, Veterans, and the general public.

Funding

Funding for the PRORP is provided by congressional appropriation and is summarized in Table 1 below:

Year	Funding
2009	$112,000,000
2010	$22,500,000
2011	$24,000,000
2012	$30,000,000
2013	$30,000,000
2014	$30,000,000
2015	$30,000,000
2016	$30,000,000
2017	$30,000,000
Total	**$338,500,000**

Table 1. Amount of Congressional Appropriation to the PRORP by Fiscal Year

The overall program investment from program inception (FY09) to FY15 is presented by general research category in Figure 1. Broadly, approximately 54% of the portfolio is composed of research projects involving interventional clinical trials or retrospective clinical research; topics that affect current clinical care or are close to clinical implementation. The remaining 46% of the investment consists of animal-specific orthopaedic and trauma model topics (e.g., heterotopic ossification [HO] or blast injuries) and the development of technology or drugs/drug targets. Many of these projects intend to better understand biology in ways that cannot be studied in humans or are early-stage projects that will seed the development of novel technologies toward clinical implementation.

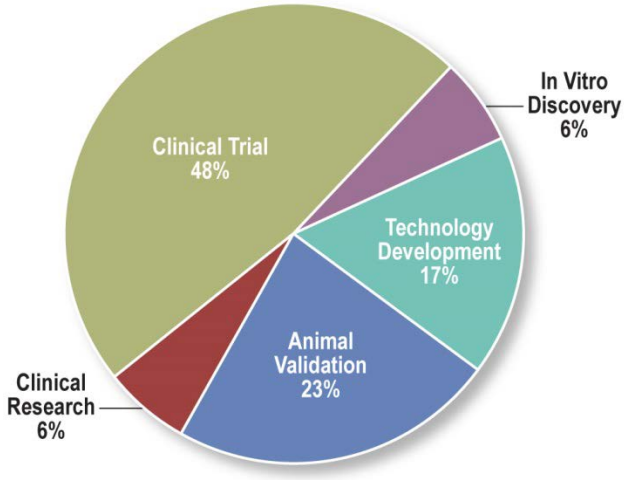

Figure 1. Overall Program Investment by Research Category for the PRORP, FY09-FY15

Management and Oversight

The PRORP is one of several research programs within the CDMRP organization. The CDMRP uses a two-tier review process for application evaluation, with both tiers employing dynamic interaction among scientists and consumers (a patient, survivor, family member, and/or caregiver of people living with the disease, injury, or condition of interest). For the PRORP, consumers include amputees, persons who have undergone limb salvage surgery, others affected by traumatic extremity injuries, and their caretakers. Consumers are involved in both tiers of review to ensure patient perspectives are represented across the continuum of review. The first tier of evaluation is a scientific peer review of research applications measured against established criteria to determine scientific and technical merit. This first review is conducted by a Peer Review Panel composed of peer scientists and clinician researchers in the relevant fields, and consumers. The Peer Review Panel is also charged with providing an estimate of the quality and feasibility of each application, as well as identifying any issues or limitations that were not addressed within the research application.

The second tier of evaluation is a comparison-based programmatic review conducted by a Programmatic Panel of subject matter experts and consumers that make recommendations for funding based on scientific merit (based on peer reviewers' ratings and comments) and on relevance to the mission of the Defense Health Program and the PRORP.

The PRORP Programmatic Panel includes representatives with either orthopaedic surgery or rehabilitation expertise from the Army, Air Force, and Navy, as well as the Department of Veterans Affairs (VA), and specialists in acute and chronic care from MTFs, such as the Walter Reed National Military Medical Center. Program funding decisions are based on current clinical and military needs, prior investments, and the quality of applications received.

Once a project has been funded, PRORP Science Officers manage the award on behalf of the US Army Medical Research Acquisition Activity Contracting Office to ensure the research is compliant with all necessary regulations, is moving forward according to the statement of work, and is on track to deliver the anticipated research outcome(s) or deliverable(s). Science Officers also work closely with several other offices within the DoD to facilitate project goals and consider possible avenues for further development of the researcher's intervention or technology.

Evolution of Investment

The large initial investment in 2009 allowed the PRORP to fund research focused on basic science projects for bone regrowth, prevention of HO, and tissue engineering. In 2010 and 2011, the PRORP supplemented this strategy by funding two major consortia to address both surgical and rehabilitation issues related to the care of and recovery from traumatic extremity injuries. In 2012, the program adopted an investment strategy that included a focus on both translational science and clinical studies. This strategy has generally been followed since 2012, although the program focus areas have continued to evolve. As the program matured, focus shifted from seeding the field with basic science technologies to research projects advancing knowledge

products (e.g., CPGs, evidence supporting specific treatment recommendations) and near-term devices and techniques likely to have an immediate impact on clinical care of traumatic injuries.

The PRORP is unique in that it supports large clinical trials for the care of wounded Service members and Veterans, with projects specific to trauma care. There is a general lack of evidence underlying best practices in trauma care as these studies are often difficult to conduct and expensive to design and enroll. The PRORP is making a major and meaningful difference in the care of those with extremity injuries by providing funding to support and encourage clinical science for trauma care. The program is recognized by specialists and caregivers as a unique resource to support the study of topics in trauma and battlefield care for wounded Service members that may otherwise go unfunded and unaddressed.

For ease of reporting within this document, the projects in Chapter II, Research Areas, have been organized under the following five categories (rather than their originally aligned focus areas): (1) Tissue Engineering and Repair; (2) Prosthetics and Orthotics; (3) Prevention and Treatment of Complications; (4) Pain Management and Patient-Reported Outcomes; and (5) Rehabilitation and Biomechanics. The PRORP consortia efforts are discussed in Chapter III.

PRORP Statistics and Performance

The PRORP has made strategic investments in support of product development and clinical studies intended to support the care of battlefield injured and wounded Service members. Many of the studies funded in 2009 were basic science studies, and as such, most of these studies are complete. These studies generally supported technologies at very early stages of development. While some have progressed on the path to market transition, many have not.

The dissemination and adoption of knowledge products can be a slow process. Published results must be absorbed and accepted by experts in the field before incorporation into consensus statements or CPGs established at national meetings. These recommendations are then used to update the standard of care at various medical centers and/or MTFs across the country.

As the PRORP portfolio has shifted to include more clinical care projects, the time needed to evaluate the outcomes of these interventions has extended. The focus on long-term outcomes requires many of the studies to include clinical follow-up of patients up to 2 years after definitive treatment to determine whether benefits of the procedures are sustained. This extends the amount of time necessary to complete, analyze, and close the study. For example, many of the funded clinical trials from FY14 are projected to end in 2018 or 2019, but extensions may very well be requested in order to capture the long-term outcomes of the intervention. Studies involving unapproved drugs and devices typically must undergo the Investigational New Drug/Device (IND) process, requiring late-phase clinical trials, which can cost upwards of $10M-$30M depending on the specific intervention and requirements. Successful transition of these products requires investigators to identify military and/or corporate partners with the funding and resources to bring their products and findings to clinical practice if late-phase studies are required. The PRORP serves to provide funding for development and validation of promising technologies, techniques, treatments, and drugs for the injured Service member.

Investigators are encouraged to work with the DoD and industry in moving the drug or device into the commercial marketplace or into advanced development for specific military use.

Since the first PRORP-funded grant was awarded in 2010, the program has been making steady progress toward closing clinical gaps in the care of injured Service members. This summary document provides an overview of the current landscape and successes of the PRORP's 7-year portfolio. Projects within this portfolio summary are at different intervals within their periods of performance; therefore, the analysis may not completely reflect the full impact of each project on the care of Service members or the orthopaedic field. For example, the PRORP has in recent years increased its investments in clinical trial research, which sometimes requires lengthy regulatory approvals, study blinding, and extended patient recruitment periods due to the sensitive research population. Moreover, 81% of PRORP-funded clinical trials are still ongoing. Results and impacts of these and other ongoing projects are forthcoming and will be reported in future analyses.

Individual project successes are highlighted in the following chapters to provide a snapshot of the developmental stage of each project. The program staff identified 15 projects that are in the process of transitioning successful products to more advanced studies or clinical care, and 27 projects that generated knowledge products or research findings with the potential to affect the clinical care of wounded Service members. These numbers reflect essentially only closed projects funded from FY09 through FY13; most projects funded after FY13 are still open and/or are at too preliminary a stage to evaluate their final outcomes. Eight of the 15 products that have made transitions are related to the Orthotics and Prosthetics focus area, and 3 are related to the Tissue Engineering focus area.

As of June 2017, PRORP funding support has produced 276 separate peer-reviewed publications: 185 in the field of Tissue Engineering, 43 in Prevention and Treatment of Complications, and 48 spread among the remaining research categories (pain management, prosthetics and orthotics, injury prevention, rehabilitation and biomechanics, and consortia) (Figure 7 and Table 10). Funding has also supported research that has led to the filing of 79 separate patents.

The PRORP has supported a number of cutting-edge projects that cover the spectrum from treatment to rehabilitation of extremity trauma, including early phase studies for the development of therapeutics to prevent joint stiffness during recovery, in vivo cartilage regeneration, and electrostimulation to enhance tissue repair. The use of electrostimulation in pain management of neuromas is also being evaluated for potential to improve functional outcomes of combat-injured Service members post-amputation and to decrease the dependency on opioid treatments. The program also has supported large clinical studies focusing on enhancing and validating effective rehabilitation for injured Service members and developing new criteria for treating major extremity trauma. Ultimately, the PRORP is seeking to impact the current CPGs and acceptable use criteria related to the diagnosis and treatment of extremity trauma and subsequent rehabilitation.

Capability Gaps and Research Goals

One of the goals of the PRORP is to identify and support research that aligns with both the Army and Defense Health Program capability gaps through coordination with the Combat Casualty Care Research Program/Joint Program Committee 6 (CCCRP/JPC-6) and the Clinical and Rehabilitative Medicine Research Program (CRMRP)/JPC-8. CCCRP and CRMRP representatives have seats on the PRORP Programmatic Panel to ensure that the capability gaps of both programs are integrated into the PRORP focus areas when determining the investment strategy that support the needs of the DoD. The JPCs organize their investments into portfolios that allow them to identify and close capability gaps that relate to the care of wounded Service members and battlefield medicine. The work in the PRORP primarily supports the Forward Surgical, En Route, and Critical Care portfolios in JPC-6. For JPC-8, the work funded by PRORP supports the Neuromusculoskeletal Injuries, Pain Management, and Regenerative Medicine portfolios. Where possible and reasonable, the PRORP focus areas align with and/or complement the capability gaps within these portfolios. The major capability gaps, as of June 2017, in these portfolios are listed below:

Clinical and Rehabilitative Medicine Research Program

Capability Gaps Relevant to the PRORP from 2015 to Present

Neuromusculoskeletal Injuries Rehabilitation Portfolio

- Limited understanding of the management throughout the rehabilitation process following neuromusculoskeletal injury
  - Inadequate evidence to determine the optimal dose, timing, frequency, duration, setting and use of innovative rehabilitative techniques to minimize impairments, maximize function and performance, and/or achieve optimal quality of life
  - Limited understanding of potential confounds to optimal rehabilitation factors that may adversely affect rehabilitation outcomes (sleep, stress, nutrition, hydration, smoking, patient compliance)
- Limited current technologies, including prosthetics and orthotics, for the rehabilitation or replacement of function that optimize patient interaction, usability, and durability.
- After primary neuromusculoskeletal injury, there is limited ability to predict, prevent, and mitigate development of secondary health deficits
- Lack of validated metrics that effectively assess initial presentation, rehabilitation, and reintegration following neuromusculoskeletal injury

Pain Management Portfolio

- Inadequate systems to examine population-based patient outcomes across time and environment (patient reported, best practices, provider reported, data mined)
- Lack of evidence for approaches to pain management for military populations for different types of pain in different settings
- Lack of evidence of what pain management strategies work for whom and under what conditions
- Lack of evaluation of implementation strategies for pain management
- Inadequate methodologies to adequately evaluate pain management techniques in clinical trials

Regenerative Medicine Portfolio

- Inadequate ability to regenerate functional neural pathways
  - Inability to maintain receptive distal end organ interface
  - Inability to control rate of peripheral nerve regeneration
  - Inability to functionally regenerate peripheral (afferent and efferent) nerve defects
- Inadequate ability to regenerate and integrate functional muscle units
  - Inability to regenerate neuromuscular interface
  - Inability to regenerate musculotendonous junctions
  - Inability to regenerate large volume vascularized muscle
- Inadequate ability to regenerate functional bone tissue
  - Inability to adequately control bone formation
  - Inability to adequately restore functional bone
  - Lack of understanding of the mechanism of heterotopic ossification

Combat Casualty Care Research Program

Defense Health Program Combat Casualty Care ICD[3] Medical Research Capability Gaps from 2015 to Present

- **Developmental Knowledge (DK)**
  - Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients
- **Identify and Manage Fractures/Wounds (IMFW)**
  - Limited ability to stabilize long-bone fractures for extended transport in the pre-hospital environment that promotes future healing and reduces incidence of complications (such as HO and fracture non-union)
- **Prevent Loss of Use of Limb(s) (PLUL)**
  - Inadequate psychosocial interventions for individuals with severe bodily distortion (e.g., limb loss, burns, facial trauma, and genital/urinary loss from complex dismounted blast injury)
  - Insufficient understanding of the differences in long-term psychological and functional outcomes of primary amputation vice dysfunctional extremity retention
  - There is a lack of understanding of the long-term quality of life impact of initial (within the first year) treatment among individuals with limb amputations
  - There is insufficient understanding of the impact of vascular disruption, repair, extremity ischemia and reperfusion and its relationship to long-term limb recovery and function
    - Lack of a standardized, clinically relevant decision support model for severely mangled extremities (i.e., decisions regarding primary amputation vs. pursuit of limb salvage, optimal amputation level to support future treatment (i.e., transplant, prosthetic, etc.)
  - Insufficient knowledge (e.g., immune suppression, etc.) and technologies (e.g., modulation, etc.) to facilitate auto- and allotransplantation of tissues and (potentially) functional limbs to support advanced reconstruction modalities
  - Lack of good upper extremity prosthetics and amputation solutions (arm, hand, etc.)

The alignment of PRORP projects with these care gaps for wounded Service members is highlighted and discussed throughout the Portfolio Summary.

[3] International Classification of Diseases

The remainder of the Portfolio Summary provides an overview of each of the five research areas within the PRORP (Chapter II) and discusses the progress made by the PRORP-funded consortia efforts (Chapter III). The summary concludes with a discussion of the PRORP Program Outcomes to provide a brief overview of the academic productivity of the projects funded by the PRORP, including presentations, publications, and patents (Chapter IV).

II: Research Areas

Tissue Engineering and Repair

Overview

Since October 2001, Soldiers of the US military have sustained 58,803 casualties in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) including 6,757 deaths and 52,046 wounded.[4] Due to the extensive use of improvised explosive devices (IEDs), a disproportionately large number of casualties are traumatic orthopaedic injuries involving the extremities that are survivable due to the widespread use of pre-hospital tourniquets and rapid air-evacuation systems.[5,6] These severe extremity injuries are in many ways unique compared to civilian equivalents because of the extensive tissue damage caused by blast injuries. While civilian trauma often also results in tissue loss, the magnitude of the damage can be much more significant in wartime injuries. It is not uncommon to find combat extremity injuries that involve multiple tissue types including bone, cartilage, tendon, muscle, fat, nerve, and blood vessels. Often the tissue is damaged beyond repair or involves a significant segmental defect, rendering the limb non-functional and necessitating amputation. Recovery often involves a difficult choice between two options, early limb amputation or an extended period of treatment, that could result in limb salvage or later amputation.[7,8] Improved methods are needed to bridge large gaps in injured bone and tissue, heal nerves, and regenerate functional muscle units.

Peripheral nervous system injuries are estimated to make up approximately 55% of combat wounds sustained in OIF and OEF.[7] One of the key determinants for lower extremity amputation is concomitant nerve injury.[9] Similarly for upper extremity injuries, segmental nerve loss with bone and vascular injury is often an indication for amputation. Taken together, these issues provide rationale to develop improved tissue engineering strategies for lower and upper extremity repair to reduce the need for amputation and increase repair capabilities of the severely

[4] https://dcas.dmdc.osd.mil/dcas/pages/casualties_oef.xhtml
[5] Holcomb JB, Stansbury LG, Champion HR, et al. 2006. Understanding combat casualty care statistics. *J Trauma* 60(2):397-401.
[6] Kragh JF Jr., Walters TJ, Baer DG, et al. 2009. Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Annals of Surgery* 249(1):1-7.
[7] Stansbury LG, Branstetter JG, and Lalliss SJ. 2007. Amputation in military trauma surgery. *J Trauma* 63(4):940-944.
[8] https://www.publichealth.va.gov/epidemiology/reports/health-care-use-gulfwar-oefoifond/index.asp
[9] Cross JD, Ficke JR, Hsu JR, et al. 2011. Battlefield orthopaedic injuries cause the majority of long-term disabilities. *J Am Acad Orthop Surg* 19 Suppl 1:S1-7.

injured extremity. The PRORP has supported research in basic and translational tissue engineering and repair technologies to address the needs of the nation's injured Warfighters, and the need of the military surgeons and medical personnel who are charged with their care and well-being.

Guided by the expertise of both the Peer Review and Programmatic Review panel members, the PRORP has made approximately $61.7M in investments, or 36% of its entire portfolio, in novel tissue engineering technology since FY09. The number of projects per year and annual investment are summarized below in Figure 2. The PRORP has invested in research projects with an aim of improving function and restoring Service members' quality of life and activity level as close to pre-injury state as possible.

Research supported by the PRORP has resulted in patents, the generation of novel treatment devices and methods, and has helped basic research advance into clinical trials. Research project highlights include a patent for Bone Tape technology used to stabilize bone in craniomaxillofacial (CMF) injuries, using beta tricalcium phosphate tethered to bone morphogenetic protein (BMP2) to increase proliferation of self or donor mesenchymal stem cells (MSCs), a novel biomedical device that applies tensile loading to a severed nerve to accelerate peripheral nerve regeneration, and several projects focused on improved treatment of cartilage, bone, and nerve injuries that have the potential to influence CPGs.

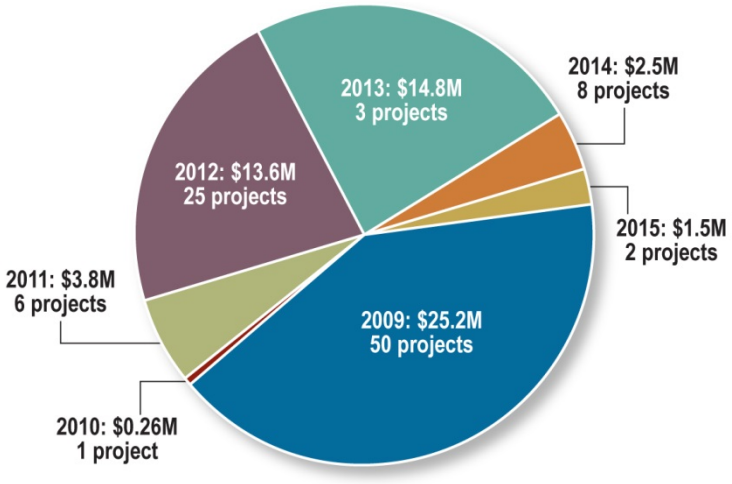

Figure 2. PRORP Investment, Including the Number of Projects Funded, by Fiscal Year for Tissue Engineering[10]

[10] Data do not include consortia projects.

Table of Highlighted Research Projects

Project Accomplishment	Principal Investigator	Log Number
siRNA Technology Prevents Scar Formation in Tendon Repair: Data from this study support the use of antisense oligonucleotides to improve flexor tendon repair and suggest that modulation of the TGF-β1 signaling pathway can reduce adhesions while maintaining the strength of the repair.	Regis O'Keefe	OR090244
Novel dSRC Cells Embedded in Photo-Crosslinkable Hydrogels Successfully Produce Hyaline Cartilage in the Knee Joint: Demonstrated that dynamic self-regenerating cartilage embedded in photochemically crosslinked collagen successfully engineers contiguous hyaline articular cartilage in the knee joint in both non-load-bearing and load-bearing environments.	Mark Randolph	OR090275
Enhanced Healing of Segmental Bone Defects by Modulation of the Mechanical Environment: Development of a "reverse dynamization" process where fixation starts with low stiffness and increases after 14 days to accelerate healing in a rat model.	Christopher Evans	OR090468
Stem Cell-Based Neurotrophic Enhancement of an Aligned Nanofiber Scaffold for Nerve Gap Repair: Mesenchymal progenitor cells facilitate early nerve growth across the injury gap and could be useful as a cellular therapy to promote peripheral nerve regeneration.	Rocky Tuan	OR090539
Novel Device Utilizes Mechanical Loading to Stabilize and Regenerate the Peripheral Nerve: Developed a novel biomedical device to apply tensile loading to severed nerve.	Sameer Shah	OR090669
Novel Device, Bone Tape, Is Developed for Stabilization of Traumatic Craniofacial Injuries: Developed "Bone Tape" for CMF bone stabilization.	Cari Whyne	OR090701
Assisted Bone Regrowth Engineering Advanced Materials for Tissue Regeneration: Demonstrated that coating beta tricalcium phosphate with protein product TCPBP-HRG leads to increased proliferation of bone marrow stem cells in vitro.	Luis Alvarez	OR100038
Large Extremity Peripheral Nerve Repair: No differences were observed between sutured, sealed allograft and autograft in rat and swine models of peripheral nerve injury.	Robert Redmond	OR110135
Combination Therapies for the Mitigation of Musculoskeletal Pathologic Damage in a Novel Model of Severe Injury and Disuse: Daily resistance exercise regimen prevented the loss in muscle volume that is caused by immobilization in a rat burn model.	Charles Wade	OR120033
Accelerating Peripheral Nerve Regeneration Through Spatial Signaling: Identified small molecule targets to accelerate axon growth.	Jeff Twiss	OR120042

Project Accomplishment	Principal Investigator	Log Number
Optimizing Soft Tissue Management and Spacer Design in Segmental Bone Defects: The Masquelet Technique significantly improves the extent and rate of bone healing in a goat fracture model.	George Muschler	OR120082
Acceleration of Regeneration of Large-Gap Peripheral Nerve Injuries Using Acellular Nerve Allografts plus Amniotic Fluid-Derived Stem Cells (AFS): Preliminary results indicate that acellular nerve allografts seeded with AFS retain viability following implantation into a nerve defect and offer improved outcomes compared to unseeded nerve allografts for segmental nerve defect repairs.	Thomas Smith	OR120157
Prevention of the Post-Traumatic Fibrotic Response in Joints: Extracellular processes associated with excessive formation of fibrotic tissue represent a valid target for limiting post-traumatic joint stiffness.	Andrzej Fertala	OR120205
Development of Class II Medical Device for Clinical Translation of a Novel PEG Fusion Method for Immediate Physiological Recovery After Peripheral Nerve Injury: A polyethylene glycol (PEG) suture device was developed to increase distal axon number. The device could also be fabricated and used in the operating room.	Wesley Thayer	OR120216

Table 2. Sampling of the PRORP Research Projects Accomplishments Within the Tissue Engineering and Repair Research Area

Prosthetics and Orthotics

Overview

Orthotic and prosthetic technology is of critical importance to the Service members who sustain orthopaedic injuries. A working paper from the Congressional Budget Office provides insight into the burden of disease facing the US military in terms of combat amputations.[11] In OIF, 3,482 hostile deaths occurred among US military personnel, and 31,947 Service members were wounded in action. Similarly, during OEF, approximately 1,800 hostile deaths occurred, with approximately 20,000 individuals wounded in action. Survival rates of the wounded were approximately 90%. Of those wounded, 2.6% suffered an amputation (or approximately 1,300 individuals out of 50,000 wounded). Combat-related limb amputation is more likely to involve multiple limbs than civilian amputation and is also more likely to involve the lower extremities than the upper extremities.

The Amputee Coalition (https://www.amputee-coalition.org/) reports estimates of approximately 185,000 amputations per year in the United States, with an estimated annual hospital cost of

[11] https://www.cbo.gov/sites/default/files/113th-congress-2013-2014/workingpaper/49837-Casualties_WorkingPaper-2014-08_1.pdf

more than $8 billion. Nearly half of individuals who undergo amputation as a result of vascular disease will die within 5 years. Fifty-five percent of those who have a lower extremity amputation due to diabetes will require a second limb amputation within 2-3 years. While civilian amputee cases make up the majority of the yearly health burden financially, the treatment needs of both civilian and active duty/Veteran amputees share similarities. Both groups are at risk for complications, including skin breakdown/infection, poor prosthetic fit and alignment, reduced physical activity, and long-term secondary health effects that develop from reduced physical activity. The research supported by the PRORP focuses on increasing activity and quality of life for patients and helping patients avoid the long-term sequelae of their amputation. Much of the research in the PRORP portfolio represents technology development to provide first-in-human data for prosthetic innovations designed to improve the ruggedness and reliability of patient prosthetics. Given the cost and complexity of some of the devices, subsequent device development/refinement or clinical trials may be required before moving the product to market. Development and support of these technologies by the DoD are critical to catalyzing those transitions.

Novel orthotic and prosthetic devices are typically US Food and Drug Administration (FDA) Class II devices and must demonstrate safety without necessarily proving efficacy before market release. However, commercialization and market impact of these devices is limited by several factors. These devices, for example, require large production volumes to be profitable to the companies developing them. Investigators may abandon even promising devices if the targeted market is too small to justify continued development or market approvals. The Centers for Medicare and Medicaid Services will not justify increased reimbursement for a new device without data showing long-term benefit in the Medicare population. Although this creates major cost and data barriers to the clinical transition of many prosthetics and orthotics developed in part by PRORP funding, the program does work with other entities within the DoD to consider advanced development of the technologies for military and/or VA use.

Guided by the expertise on both the Peer Review and Programmatic Review Panels, the PRORP has invested approximately $30.8M (18% of the portfolio) in novel prosthetic and orthotic technology research from FY09 to FY15. The number of projects per year and annual investment are summarized below in Figure 3.

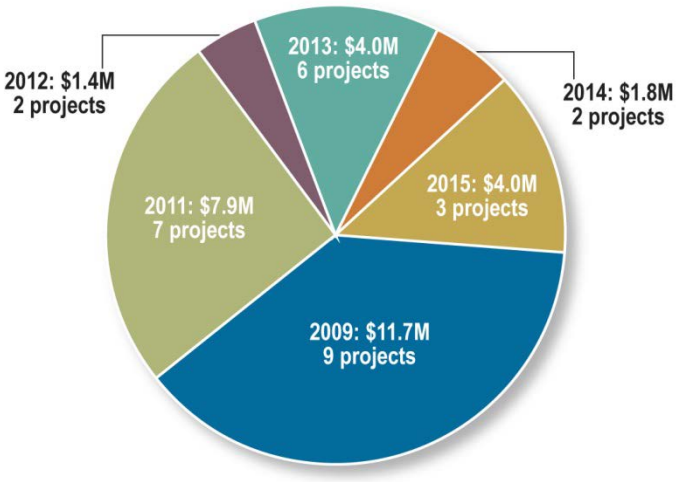

Figure 3. PRORP Investment, Including the Number of Funded Projects, by Fiscal Year for Orthotic and Prosthetic Technology[12]

The PRORP has funded projects in the design and development of novel, rugged upper and lower extremity prosthetics, objective methods of measuring prosthetic fit and function, measurements of patient treatment compliance, and powered prosthetics – all with an aim of restoring function and improving quality of life, with the ultimate goal of returning Service members to duty if they so choose. PRORP-funded projects include the development of a socket with a more uniform stress distribution for transfemoral amputations, as well as a lower-limb prosthetic cooling system, Intra-socket Cooling Element (ICE). PRORP-funded research also has resulted in the development of several feedback sensors that can respond to volume changes at the interface of the prosthetic device and residual limb, e.g., the ECHO®, a dynamic impedance sensor system, and an integrated monitoring system that uses a combination of shear and normal force sensors with compressed gas technology. Furthermore, PRORP-funded projects have helped generate cable actuated robotic hands that allow for more highly functional grasping.

Table of Highlighted Research Projects

Project Accomplishment	Principal Investigator	Log Number
Mobile Gait Analysis System for Lower Limb Amputee High-Level Activity Rehabilitation: A mobile gait analysis system was developed to gather real-time data on prosthetic fit and function during use in the real world.	Nance Ericson	OR090035
Development of Sub-Ischial Prosthetic Sockets with Vacuum-Assisted Suspension for Highly Active Persons with Transfemoral Amputations: A new socket forming technique was developed and is used in clinical practice.	Stefania Fatone	OR090122

[12] Data do not include consortia projects.

Project Accomplishment	Principal Investigator	Log Number
In-Socket Monitoring of Limb Volume for Maintenance of Limb Volume/Mass: The ECHO® system was developed to accommodate residual stump volume changes.	Joan E. Sanders	OR090142
High Performance Prosthetic Socket with Proprioceptive Haptic Feedback and Prognostic Pressure Monitor: Developed three-axis optical tactile sensor and flexible bladder for prosthetic use.	Jason Wheeler	OR090333
Compliance and Adaptive Underactuation for Prosthetic Terminal Devices: Developed a low-cost, cable-actuated prosthetic hand prototype for highly functional grasping.	Aaron M. Dollar	OR090671
A New Powered Flexion Wrist and Modular Prosthesis System: Finished a prosthetic product called the Force Limiting Auto Grasp (FLAG) and modified the Electric Terminal Device (ETD) by Motion Control to produce a 3 degrees of freedom prosthetic wrist called ETD2.	Harold H. Sears	OR110079
Development and Clinical Trial of an Insole Sensor to Determine Optimal Limb Loading in the Rehabilitation of Open Tibia Fractures: ATLAS (Ambulatory Tibial Load Analysis System) was developed to measure foot loads, which could be used to study the effect of compliance and weight bearing on fracture healing.	Erik N. Kubiak	OR110121
Clinical Trials of Pattern Recognition, Electrode Grid, RIC[13] Arm in TMR[14] Subjects: Comparing direct control with pattern recognition control of the robotic arm after targeted muscle reinnervation surgery.	Todd Kuiken	OR110187
Development of Moisture Management Liner and Active Cooling System for Improving Residual Limb Skin Care: Designed the ICE, an active cooling system that uses electrical current to cool the residual limb within the prosthetic.	Gordon B. Hirschman	OR120169
An Innovative Residual Limb-Lengthening Device: Designed an intramedullary rod that can be surgically implanted to increase the length of a short residual limb for a transfemoral amputee.	Todd Kuiken	OR130080
Prosthetic Fit Assessment in Transtibial Amputees Secondary to Trauma (ProFit): Fit data are collected using smart pyramid on Transtibial Amputation Outcomes Study (TAOS) patients from METRC to produce a validated measure of fit for prosthetics.	Saam Morshed	OR130357

Table 3. Sampling of the PRORP Research Projects Accomplishments Within the Prosthetics and Orthotics Research Area

[13] Rehabilitation Institute of Chicago
[14] Targeted Muscle Reinnervation

Prevention and Treatment of Complications

Overview

Service members exposed to blast and orthopaedic injury are highly susceptible to complications including HO and post-traumatic osteoarthritis (PTOA), among others, resulting in lifelong reductions in daily activity levels and overall health. HO describes the presence of bone, or bone formation, in soft tissue where bone normally does not exist. PTOA is a form of osteoarthritis (wearing away of the cartilage in the joint) that occurs after trauma to the joint. Both conditions can impair an individual's ability to use his/her prosthesis, mobility, and independent care of oneself. There are as many as 900,000 knee injuries annually in the United States that may lead to PTOA.[15] It is estimated that post knee injury, the rate of PTOA can be as high as 8.27 cases per 1,000 active duty military personnel.[16] Improved methods for the management of these complications are critically needed. The projects discussed in this chapter represent strategic investments that the PRORP has made in understanding the biology that results in these complications and technologies for addressing them.

The PRORP has made approximately $57.5M (34% of the portfolio) in investments in Prevention and Treatment of Complications over its history. The number of projects per year and annual investment are summarized below in Figure 4.

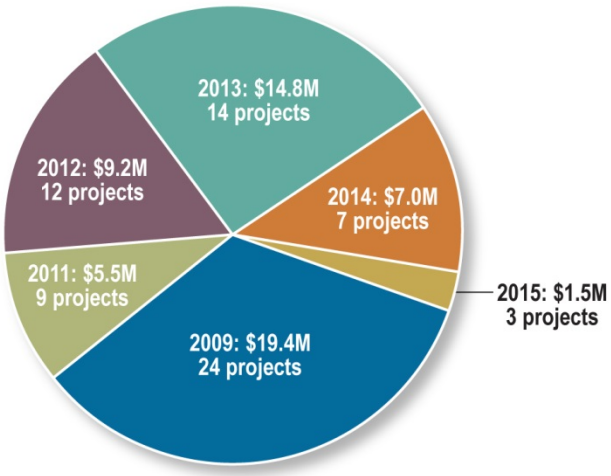

Figure 4. Breakdown of PRORP Investment in Prevention and Treatment of Complications, Including the Number of Projects Funded by Fiscal Year[17]

[15] Lotz MK and Kraus VB. 2010. New developments in osteoarthritis: Posttraumatic osteoarthritis: pathogenesis and pharmacological treatment options. *Arthritis Res Ther* 12(3):211
[16] Thomas AC, Hubbard-Turner T, Wikstrom EA, et al. 2017. Epidemiology of posttraumatic osteoarthritis. *J Athl Train* 52(6):491-496.
[17] Data do not include consortia projects.

Table of Highlighted Research Projects

Project Accomplishment	Principal Investigator	Log Number
Heterotopic Ossification Following Extremity Blast Amputation: An Animal Model in the Sprague Dawley Rat: Pulse lavage contributed to the formation of HO in a rat model, while bulb syringe irrigation did not.	Vincent Pellegrini	OR090278
A Clinically Realistic Large Animal Model of Intra-Articular Fracture: This project sought to develop and validate a swine model of intra-articular fracture (IAF) and PTOA and evaluate antioxidants for the treatment of PTOA.	Jessica Goetz	OR090331
Diagnosis of Compartment Syndrome Based on Tissue Oxygenation: Phenylephrine with or without fasciotomy was equally efficient at preventing compartment syndrome in a dog model.	Hubert Kim	OR090580
Battlefield-Acquired Immunogenicity to Metals Affects Orthopaedic Implant Outcome: Retained metal in Service members led to metal reactivity/hypersensitivity.	Nadim Hallab	OR090690
Development of Intra-Articular Drug Delivery to Alter Progression of Arthritis Following Joint Injury: Local delivery of IL-1Ra following IAF reduced severity of arthritis in a mouse model.	Steven Olson	OR090702
Fluid Lavage of Open Wounds (FLOW): A Multicenter, Blinded, Factorial Trial Comparing Alternative Irrigating Solutions and Pressures in Patients with Open Fractures: The study used a 2x3 factorial design looking at three irrigation pressures and two different solutions (saline and soap) for irrigation and debridement after open fracture. All groups had similar efficacy.	Kyle Jeray	OR110030
Early Identification of Molecular Predictors of Heterotopic Ossification Following Extremity Blast Injury with a Biomarker Assay: Potential gene signatures for early- and late-stage HO development from data generated thus far from a rat model.	Vincent Pellegrini/ Leon Nesti	OR120071/ OR120071P1
Peripheral Nerve Repair and Prevention of Neuroma Formation: Two drug agents were identified, cromolyn and a B3 adrenergic receptor antagonist L-743,337, that prevent neuroma formation. Cromolyn also prevented HO formation.	Alan Davis	OR120168
Evaluating Efficacy of Novel Therapeutics for Mitigating Post-Traumatic Osteoarthritis: Demonstrated that recombinant Sost protein may be used therapeutically to prevent cartilage degradation.	Gabriela Loots	OR130220
Cellular Source of Adult Articular Cartilage Maintenance and Repairs: Identified lubricin-expressing cells in the superficial zone of the articular cartilage, which invade the microfractured area and reconstitute hyaline cartilage at the site of injury.	Hong Mei	OR130235

Table 4. Sampling of the PRORP Research Projects Accomplishments Within the Prevention and Treatment of Complications Research Area

Rehabilitation and Biomechanics

Overview

Injured Service members collectively represent a large group of young, otherwise healthy, individuals with strong motivation to return to high-functioning levels of activity, work, and active duty. A retrospective analysis of all US military personnel who sustained a combat-related amputation between October 1, 2001 and June 1, 2006 revealed that the average age of amputees returning to duty and separated from service was 31.4 and 27.2, respectively.[18] Although these injured Service members are receiving the best in rehabilitative care and technology, per current guidelines, the long-term health outcomes are not always clear. In addition, recent medical advances have allowed for more successful limb salvage surgeries; therefore, damaged limbs that would have previously been amputated are now candidates for salvage. The field needs more condition-specific rehabilitation strategies focused on this population that wish to return to and maintain an active lifestyle.

RTD rates for Service members with an amputation sustained while on active duty improved from 2.3% in the 1980s to 16.5% in the early 2000s.[12,19] The rates of major limb amputation in current conflicts in Afghanistan and Iraq indicate higher rates of amputation for lower extremity injuries (8.5%) compared to upper extremity injuries (3.1%), with above- and below-the-knee amputations constituting over 50% of the major limb amputations.[20] In addition, approximately 18.3% of Service members who sustain a Type III open tibia fracture on active duty and undergo limb salvage or amputation are RTD.[15] As surgical techniques, tissue repair capabilities, and prosthetic devices evolve, so must the rehabilitation strategies that optimize the success of the new interventions to further improve the RTD rate for injured Service members.

Since FY09, the PRORP has made approximately $8.9M (5% of the portfolio) in investments in rehabilitation and biomechanics. The number of projects per year and annual investment are summarized below in Figure 5.

[18] Stinner DJ, Burns TC, Kirk KL, et al. 2010. Return to duty rate of amputee soldiers in the current conflicts in Afghanistan and Iraq. *J Trauma* 68(6):1476-1479.
[19] Cross JD, Stinner DJ, Burns TC, et al. 2012. Return to duty after type III open tibia fracture. Skeletal Trauma Research Consortium. *J Orthop Trauma* 26(1):43-47.
[20] Stansbury LG, Lalliss SJ, Branstetter JG, et al. 2008. Amputations in U.S. military personnel in the current conflicts in Afghanistan and Iraq. *J Orthop Trauma* 22(1):43-46.

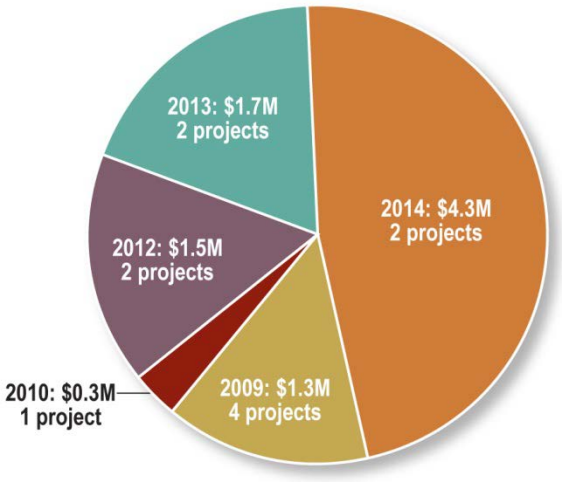

Figure 5. PRORP Investment and Number of Funded Projects by Fiscal Year for Rehabilitation and Biomechanics[21]

The PRORP has invested in novel research projects, all with the aim of improving the quality of life for Service members and restoring activity to a pre-injury state. Since 2009, PRORP-funded studies have identified two virtual stress testing (VST) metrics that have a strong association with clinical adverse events of non-union occurring within 2 months of fixator removal using non-invasive biomechanical computed tomography (BCT). In addition, PRORP studies focused on rehabilitation and biomechanics led to the development of a prototype modular functional fracture brace that stabilizes the fracture without causing soft tissue injury. This particular prototype can be applied in the field with lightweight, compact, and transportable instruments and be used in Role 1 (Point of Injury Care) or Role 2 (Medical Companies) to stabilize a patient prior to transport.

Table of Highlighted Research Projects

Project Accomplishment	Principal Investigator	Log Number
Virtual Stress Test of Healing Fractures: This is the first attempt to apply computed tomography (CT)-derived VST clinically to provide an objective prediction of clinical failure associated with fracture healing and identifying tibia-fracture patients who can safely have their fixator frame removed.	Leon Nesti	OR090474
The Role of Soft Tissue in Fracture Fixation Stability of Upper and Lower Extremity: Functional bracing was compared to plate/rod fixation in cadaveric slot defects, and data support the use of external fixators for stabilization during evacuation to a field hospital.	Elizabeth Ouellette	OR090660

[21] Data do not include consortia projects.

Project Accomplishment	Principal Investigator	Log Number
microRNA, Angiogenesis, and Skeletal Anabolic Response to Mechanical Strain: Demonstrated that a targeted deletion of the miR17-92 cluster reduced longitudinal growth as well as bone size and is critically involved in mediating the increased bone growth induced by mechanical loading in a mouse model.	Chandrakesekar Kesavan	OR090703

Table 5. Sampling of the PRORP Research Projects Accomplishments Within the Rehabilitation and Biomechanics Research Area

Pain Management and Patient-Reported Outcomes

Overview

Pain management and patient-reported outcomes (PROs) are ongoing topics of interest in orthopaedic surgery. Physicians seek to better control acute pain levels, both to prevent the development of chronic pain syndromes and to help patients enter rehabilitation and return to full function more quickly after surgery. The opioid epidemic and national efforts to identify non-opioid pain treatments have also reenergized the pain management research field. Statistics from the Centers for Disease Control and Prevention indicate that 259 million prescriptions for painkillers were written by healthcare providers in 2012, which is enough for every American adult to have a bottle of pills.[22] According to the National Institute on Drug Abuse (NIDA), misuse of prescription drugs is higher among Service members than among civilians, with opioid pain medications being the most misused. In addition, NIDA reports that prescriptions for pain relievers written by military physicians increased fourfold to approximately 3.8 million between 2001 and 2009.[23]

PROs provide longitudinal data on function after surgery to document functional and quality of life improvements that come from treatment. PROs are rarely a standalone research project; investigators are, however, encouraged to include PRO assessments in their research plan or study design. While none of these topics have been specific focus areas for PRORP since 2009, the portfolio has made investments in promising related projects. These awards were funded under broader topics including the development of orthopaedically relevant in vivo models, the prevention of complications, and rehabilitation strategies to improve outcomes of severe limb injuries.

The PRORP has made approximately $11.4M (7% of the portfolio) in investments in pain management and PRO technology since it began in FY09. The number of projects per year and annual investment are summarized below in Figure 6.

[22] CDC. 2014. Opioid Pain Killer Prescribing. Retrieved from https://www.cdc.gov/vitalsigns/opioid-prescribing
[23] NIDA. 2013. Substance Abuse in the Military. Retrieved from https://www.drugabuse.gov/publications/drugfacts/substance-abuse-in-military

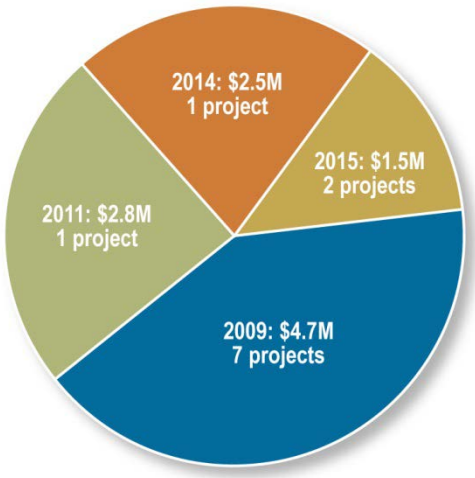

Figure 6. PRORP Investment for Pain Management and PROs, Including the Number of Funded Projects by Fiscal Year[24]

Table of Highlighted Research Projects

Project Accomplishment	Principal Investigator	Log Number
Enhancing Post-Traumatic Pain Relief with Alternative Perineural Drugs: Identified midazolam and bupivicaine as enhanced post-operative pain relief when combined with lidocaine or ropivacaine alone.	Brian Williams	OR090012
Development of a Novel Translational Model of Vibration Injury to the Spine to Study Acute Injury In Vivo: Thirty minutes of vibration for a single day at the body's resonance frequency induced behavioral changes indicative of pain in rats that were sustained for 2 weeks. Established protocols to assay for cytokines in the blood and identified a panel of pro- and anti-inflammatory cytokines associated with pain from vibration.	Beth A. Winkelstein	OR090496
Salmon Thrombin as a Treatment to Attenuate Acute Pain and Promote Tissue Healing by Modulating Local Inflammation: Wound treatment with salmon thrombin led to reduced pain and faster healing in a rat model.	Beth A. Winkelstein	OR090700
Improving Functional Outcomes of Combat-Injured Warfighters by Relieving Post-Amputation Pain Using NerveSpace Therapy: The use of percutaneous peripheral nerve stimulation (PNS) to reduce phantom and residual limb pain.	Joseph Boggs	OR110066

Table 6. Sampling of the PRORP Research Projects Accomplishments Within the Pain Management and Patient-Reported Outcomes Research Area

[24] Data do not include consortia projects.

III: Consortia

Overview of PRORP Consortia

PRORP funds have supported 32 clinical trials, most of which are multicenter efforts that allow more Service members and civilians access to potentially life-changing interventions. The PRORP also has funded two major consortia efforts in its 7-year portfolio in order to provide the infrastructure and coordination necessary to conduct large, multi-site clinical trials that will provide high-quality evidence to support CPGs to improve the care of injured Service members and Veterans. METRC (now the Major Extremity Trauma and Rehabilitation Consortium) and the BADER Consortium have been separately funded via grant awards made in 2009 (METRC2), 2010 (BADER), and 2015 (METRC3).

The PRORP made its first consortium award to METRC (METRC2) in 2009. METRC2 was funded to support a range of studies comparing controversial procedures used in the management of battlefield trauma, for example, amputation versus salvage/retention of mangled lower extremities, identification of the best amputation techniques to use for below-the-knee amputations, and the best pain management strategies to both reduce chronic pain and prevent the development of dependence on opioids. METRC competed and was selected for a second consortia award from the PRORP in 2015 (METRC3) to support studies evaluating the benefits of cognitive behavioral therapy (CBT) combined with traditional treatment to improve patient outcomes, controlled weight-bearing during fracture management and rehabilitation, and effects of different pelvic binder use on patient outcomes.

The PRORP funded the BADER Consortium with FY10 funds. The BADER Consortium focuses on rehabilitation strategies and outcomes for amputees, virtual simulations of real walking, and providing evidence-based data and prescription guides for active amputees to aid in the selection of available prosthetics. METRC and BADER Consortium efforts are further detailed in the following pages.

The intent of the consortia awards was to fund clinical studies focused on addressing questions that would improve the outcomes of severe musculoskeletal injuries commonly associated with military combat not previously investigated because they would require large, multi-site clinical trials with appropriate statistical power. In addition, the consortia awards were designed to combine the population of military orthopaedic trauma patients and the combat-relevant expertise of the specified MTFs with the patient populations and research expertise of highly qualified civilian orthopaedic trauma departments or rehabilitation scientists at outstanding institutions. METRC is currently expanding its already established networks, including polytrauma centers, to utilize the expertise of highly qualified orthopaedic trauma specialists. METRC research projects address gaps defined by the DoD to help resolve some of the major problems facing wounded Service members with severe extremity injuries; research findings from these studies can be extended to civilian trauma surgeons to care for similar injuries. BADER is a unique rehabilitation consortium with emphasis on limb salvage to better close the gap between traditional patient outcomes and optimal functional outcomes. Research findings

from the BADER Consortium will lead to higher percentages of Soldiers returning to active duty and an optimally active lifestyle, thereby reducing the risk for associated chronic conditions such as pain and osteoarthritis. Several clinical trials from the METRC and BADER consortia recently concluded and reported findings will be available for future analyses.

Major Extremity Trauma and Rehabilitation Consortium (METRC)

Background

First established in 2009 with funding from the DoD Orthopaedic Extremity Trauma Research Program (OETRP), the METRC addresses issues pertaining to the early, acute treatment of limb injuries. There have been two separate follow-on awards made in 2010 for METRC2 and 2015 for METRC3, for a total of three awards to date. As originally proposed, METRC would consist of 12 core clinical centers, 30 satellite centers, and 1 data coordinating center. METRC now partners with over 50 MTFs and civilian trauma centers that are participating in 15 ongoing studies. The consortium has created a registry of patients between the ages of 18 and 84 who were admitted with fractures requiring surgery of the upper or lower extremity, pelvis or acetabulum, and foot (calcaneus, talus, or crush injuries only). The outcomes from these studies are being used to establish treatment guidelines for the optimal care of wounded Service members. The overall goal of METRC is to improve the clinical, functional, and quality of life outcomes for both Service members and civilians that have sustained high-energy trauma to extremities. Four research studies were initiated in 2009 through the first METRC consortium award (not funded by the PRORP):

1) rhBMP-2 vs. Autograft for Treating Critical Size Tibial Defects: A Multi-Center, Randomized Trial (pTOG)
2) A Retrospective Study of the Treatment of Long Bone Defects (RETRODEFECT)
3) A Prospective Randomized Trial to Assess Fixation Strategies for Severe Open Tibia Fractures: Modern Ring External Fixators or Internal Fixation with Intramedullary Nails or Plates (FIXIT)
4) Assessment of Severe Extremity Wound Bioburden at the Time of Definitive Wound Closure or Coverage: Correlation with Subsequent Post-Closure Deep Wound Infection (BIOBURDEN)

METRC2, funded by the PRORP in 2010, includes the five additional studies listed below in Table 7. Additional information on these studies is available in the April 2017 supplement of the *Journal of Orthopaedic Trauma*, a special issue dedicated to METRC protocols.

Project Listing
Outcomes Following Severe Distal Tibia, Ankle, and/or Foot Trauma: Comparison of Limb Salvage vs. Transtibial Amputation Protocol (OUTLET)
Comparison of Transtibial Amputation With and Without a Tibia-Fibula Synostosis (TAOS)
Predicting Acute Compartment Syndrome Using Optimized Clinical Assessment, Continuous Pressure Monitoring, and Continuous Tissue Oximetry (PACS)
Improving Pain Management in High Energy Orthopaedic Trauma (PAIN)
Improving Activity and Quality of Life Following Orthopaedic Trauma: The Trauma Collaborative Care Study (TCCS)

Table 7. List of the METRC2 Projects

METRC3 was funded by the PRORP in 2015. In addition to adding several projects to the METRC portfolio, a name change occurred to capture the consortium's new commitment to rehabilitation research, Major Extremity Trauma and Rehabilitation Consortium (METRC3), previously the Major Extremity Trauma Research Consortium.

Project Listing
Measuring Patient-Specific Injury and Progression of Immunologic Response to Optimize Orthopaedic Interventions in Multiply Injured Patients (PRECISE)
Cognitive Behavioral Based Physical Therapy (CBPT): Improving Trauma Outcomes
Early Advanced Weight Bearing for Periarticular Knee and Pilon Injuries: An RCT Using the Antigravity Treadmill (AlterG)
Early Mechanical Stabilization of Bleeding in Disruption of the Pelvic Ring (EMS-BinD)
Long-Term Consequences of Major Extremity Trauma: A Pilot Study

Table 8. List of the METRC3 Projects

Capability Gap Alignment

METRC studies are specifically selected to address gaps, defined by the DoD, in the treatment and recovery of combat extremity trauma by:

1) Improving the compartment syndrome diagnosis guidelines;
2) Providing a therapy to reduce the need for fasciotomy;
3) Developing guidelines to direct the treatment (limb salvage vs. amputation) of severe distal tibia and foot trauma;
4) Defining the indications for an Ertl amputation;

5) Assessing the impact of multi-modal post injury pain control strategies; and
6) Testing new strategies to improve the long-term functional recovery and return to activity of wounded Service members.

Bridging Advanced Development for Excellent Rehabilitation (BADER) Consortium

Background

The BADER Consortium was initiated in 2011 in response to the FY10 PRORP Orthopaedic Rehabilitation Clinical Consortium Award Program Announcement. This collaboration, coordinated through the University of Delaware, brought together research efforts at the three DoD Advanced Rehabilitation Centers at Walter Reed National Military Medical Center, the Center for the Intrepid at San Antonio Military Medical Center (SAMMC), and the Comprehensive Combat and Complex Casualty Care Center at Naval Medical Center San Diego. It also combined efforts at Naval Medical Center Portsmouth, the VA Extremity Trauma and Amputation Center of Excellence, and the National Institutes of Health (NIH). Additional partners include the Mayo Clinic and Harvard Medical School. The overall goal of the BADER Consortium is to address the rehabilitation of lower limb traumatic injuries, thereby increasing the percentage of Soldiers returning to active duty and an optimally active lifestyle, which simultaneously reduces the risk for associated chronic conditions such as pain and osteoarthritis. To accomplish this goal, BADER has conducted several studies to investigate bone health in individuals with unilateral, transfemoral amputations with differing types of prosthetic devices, examine stability and balance in the walking gait of individuals with unilateral transtibial amputations, investigate optimal walking using passive dynamic orthoses for individuals with lower limb salvage procedures, and develop optimal training techniques for running to reduce injury risk in individuals with unilateral, transtibial amputation.

The BADER Consortium has initiated the six studies shown in Table 9 below.

Project Listing
Improving Step-to-Step Control of Walking in Traumatic Amputees
Prosthetic Leg Prescription (ProLegRx): What Is the Optimal Stiffness and Height of a Running-Specific Prosthesis?
Sustainable Benefits of a Power Ankle Prosthesis for Transtibial K2 and K3 Ambulators
Development of an Assessment Toolbox to Measure Community Reintegration, Functional Outcomes, and Quality of Life After Major Extremity Trauma
Maximizing Outpatient Rehabilitation Effectiveness (MORE)
Characterization of Prosthetic Feet for Weighted Walking in Service Members with Lower-Limb Amputation

Table 9. List of the BADER Projects

Capability Gap Alignment

Topic areas covered by BADER-funded projects and their emerging team research initiatives include the following DoD-identified critical gap areas to reduce the incidence of falls:

1) Retraining to improve walking and running after amputation
2) Prescribing prosthetics for work and carrying heavy loads
3) Determining the impact of robotic prosthetics on functional outcome levels and quality of life

Additional Projects Focus on:

1) Improving measures of functional outcomes
2) Determining the effectiveness of current rehabilitation care trajectories

IV: PRORP Program Outcomes

Introduction

Monitoring products generated from program funding is necessary and useful to create strategic plans for future program funding by analyzing outcomes that resulted from prior investments. This chapter provides a brief overview of the scientific and technical work products for the PRORP to include publications, presentations, and patents as reported by the funded investigators. These data not only help to monitor the progress of the funded research toward knowledge or materiel products, but also demonstrate how research findings are shared with the public to advance the field. Publications are presented by year and chapter; presentations and patent applications are presented by year. Records for FY16 and FY17 may not be complete, depending on the project's reporting and review cycle. The graphs and information presented within this portfolio summary represent data as of June 20, 2017.

Publications

The majority of the publications in the PRORP portfolio are from the Tissue Engineering and Repair, Prevention and Treatment of Complications, and Prosthetics and Orthotics investments (Figures 7 below), which is consistent with the program's early and robust funding in these areas. Additionally, many of these areas focused on animal models or bench/translational science, which produce results far more quickly than clinical research involving human participants. Many of the funded clinical trials have not yet published their results as they are still blinded and data collection is still ongoing.

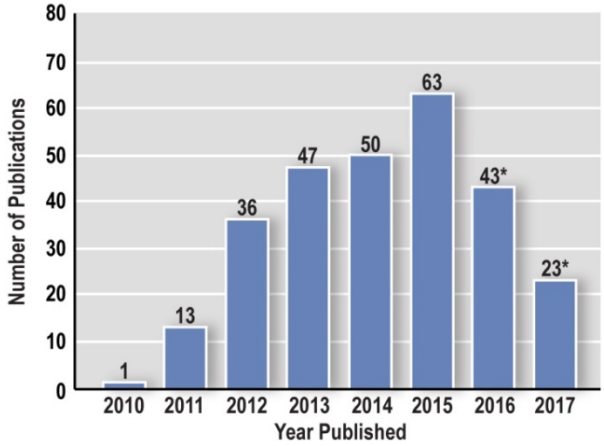

Figure 7. PRORP Publications by Year of Publication
*(*These numbers are not final and are anticipated to increase as some publications have not been received or reviewed by Program staff.)*

Funding Category	Number of Publications	Dollars Invested (in Millions)
BADER	6	$20.2
METRC	14	$52.6
Pain Management and Patient-Reported Outcomes	6	$11.4
Prevention and Treatment of Complications	43	$57.5
Prosthetics and Orthotics	13	$30.8
Rehabilitation and Biomechanics	9	$8.9
Tissue Engineering and Repair	185	$61.7

Table 10. Summary of the Number of Publications and Total Investment Dollars per Research Area from FY09 Through FY15

Presentations

The largest number of presentations reported to the PRORP was provided by Tissue Engineering and Repair projects, and many of those projects were funded with 2009 appropriations (Figures 8 and 9 below). Investigators that did not report the presentation date or meeting name are excluded from the data. The presentation and publication plots both show similar productivity trends, with the highest number of presentations in 2014 and the largest number of publications published in 2015. This appropriately reflects when the first PRORP-funded projects were nearing their project end date, allowing for analysis of data for presentation and publication submissions. As the portfolio has shifted to focus more on clinical trials, the number of presentations and publications per year has decreased due to the special circumstances of clinical

trial data reporting, including blinded or long-term studies and studies that are moving forward to the next clinical phase.

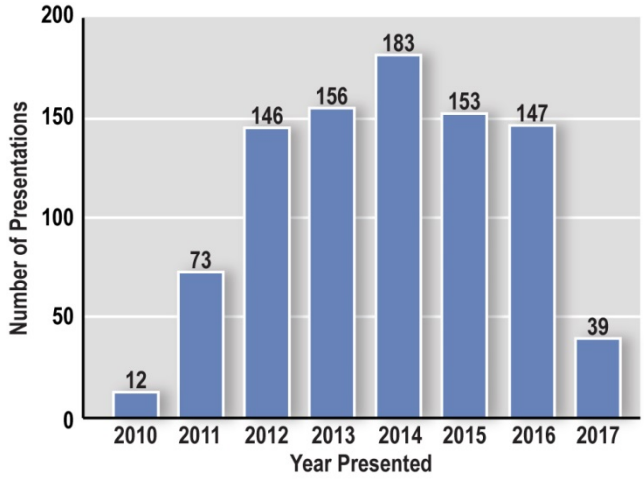

Figure 8. PRORP Presentations by Year Presented
**Presentation data as of June 2017*

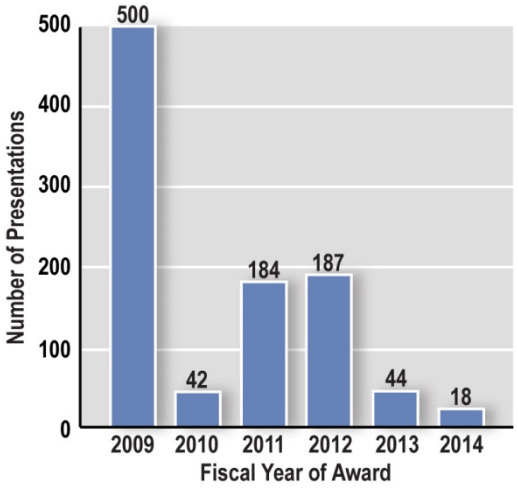

Figure 9. PRORP Presentations by Fiscal Year of Award from FY09 Through FY14

Patents

Patents show a similar trend to publications and presentations (Figures 10 and 11 below). Most patents are filed near the end of the award performance period, with nearly all of them stemming from Tissue Engineering and Repair projects awarded in 2009 (Figure 11). Clinical trials, in which the PRORP has invested heavily in recent years, generally produce knowledge products to assist in clinical care. This supports the reduction of patents filed in the most recent year in these figures.

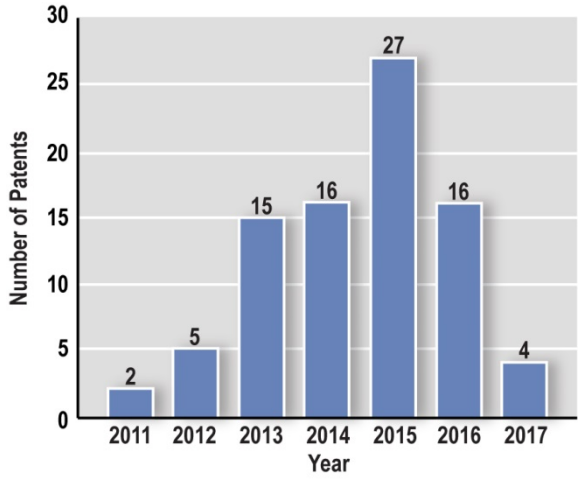

Figure 10. PRORP Patents by Year Filed

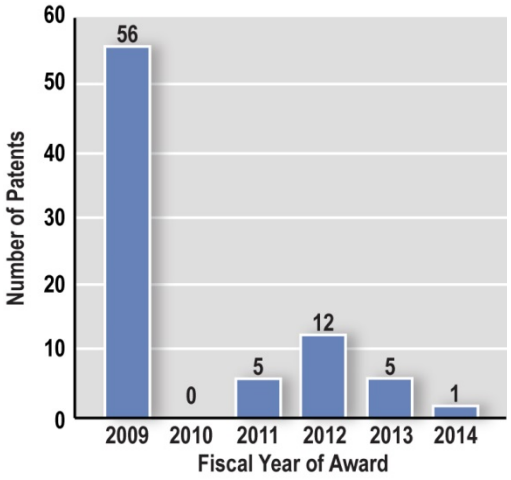

Figure 11. PRORP Patents by Fiscal Year of Award from FY09 Through FY14