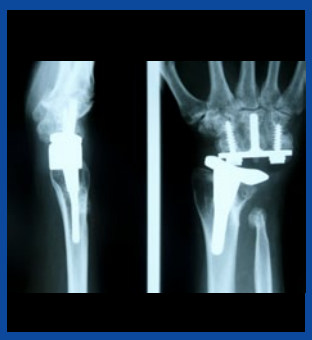
CDMRP

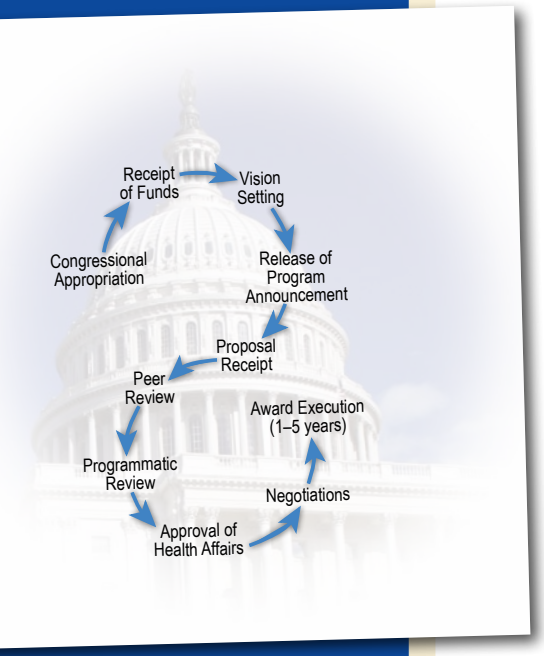
Department of Defense

Peer Reviewed Orthopaedic Research Program


U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs



History

The Congressionally Directed Medical Research Programs (CDMRP) stemmed from an effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. In fiscal year 1992 (FY92), the CDMRP office was created within the U.S. Army Medical Research and Materiel Command (USAMRMC) to execute and manage these funds, initiating a unique partnership between the public, Congress, and the military. The CDMRP has grown to encompass multiple targeted research programs, managing more than $7 billion in appropriations since its inception in FY92 through FY12. Funds for the programs are added by Congress to the Department of Defense (DoD) budget annually where support for individual research programs is allocated via specific guidance from Congress. The CDMRP executes programs, such as the Peer Reviewed Orthopaedic Research Program (PRORP), on behalf of the DoD Defense Health Program (DHP), which provides health support across the full range of military operations.

Application Review

The CDMRP program management cycle includes openly competed calls for applications and a two-tier review process recommended by the Institute of Medicine of the National Academies. Each level of review is conducted by panels composed of scientists and clinicians, who are subject matter experts, and consumers. The first tier of evaluation is an external scientific peer review of applications against established criteria for determining scientific merit. The second tier is a programmatic review conducted by members of the Integration Panel who compare submissions and make funding recommendations based on relative scientific merit, portfolio balance, and relevance to program goals. Recommendations and decisions are coordinated with the DHP Joint Program Committees to ensure alignment and complementation with military-relevant research priorities.

Consumer Advocacy Participation

A unique aspect of the CDMRP is the active participation of consumer representatives throughout the program's annual cycle. Consumers work collaboratively with leading scientists and clinicians in setting program priorities, reviewing applications, and making funding recommendations. From a unique perspective gained through personal experience—as someone with a traumatic orthopaedic injury obtained through military service—a consumer brings a sense of urgency and focus to all levels of decision making. Consumers evaluate applications based on the potential impact and benefit to the patient population, encouraging funding recommendations that reflect the concerns of patients, their families, and the clinicians who treat them.

"The DoD Peer Reviewed Orthopaedic Research Program was a fantastic experience for me as a transfemoral amputee and service-connected disabled veteran. I thoroughly appreciate the level of thought, expertise, and compassion displayed by the experts in orthopaedic research. They will undoubtedly make a difference for future generations of orthopaedic patients."

CPT R. Clayton Hinchman
Military Officers Association of America
PRORP Peer Reviewer FY11

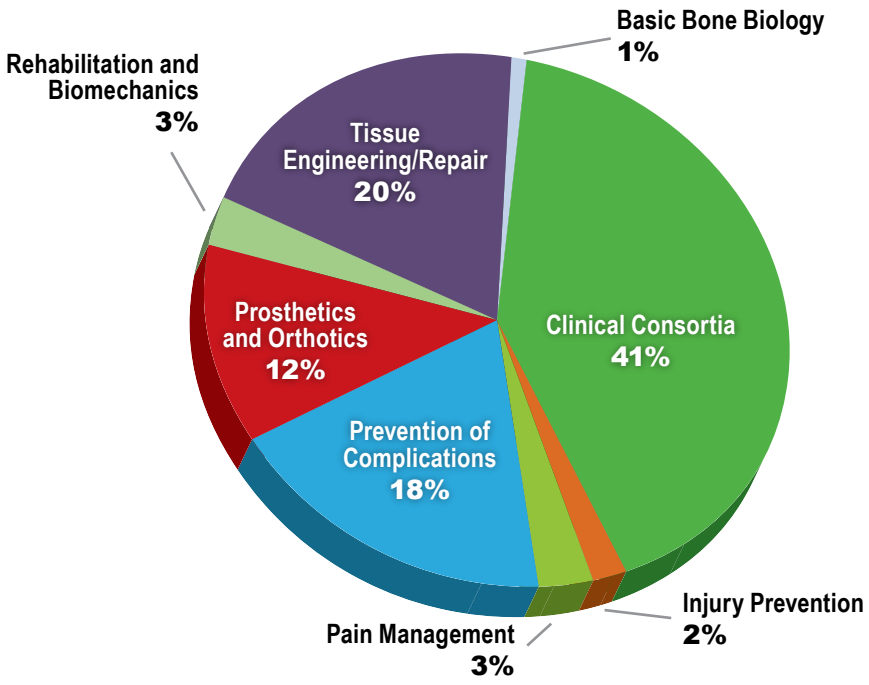
Peer Reviewed Orthopaedic Research Program

Program History

A large majority of the injuries sustained by military personnel in U.S. war efforts involve soft tissue wounds and skeletal fractures, pointing to an urgent need for orthopaedic research that will provide superior medical care and treatment options for injured service members. The PRORP was established by Congress in FY09 to support military-relevant orthopaedic research. The program has been continued each year through FY12 with congressional appropriations totaling $188.5 million (M), including an appropriation of $30M in FY12.

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. Blast and other combat-related injuries frequently involve multiple limb traumas to an extent not seen in the civilian setting and are sustained in an environment where access to optimal acute care is limited. Frequent outcomes and complications include amputation, infection, compartment syndrome, nonunion of the bone, heterotopic ossification, and temporary or permanent functional muscle loss, among others. The PRORP crafts investment strategies and funding portfolios to address these challenges with the goal of helping injured service members achieve optimal recovery from combat-related orthopaedic injuries.

PRORP Awards by Research Area and Dollar Amount, FY09–FY11



VISION

Provide all Warriors affected by orthopaedic injuries sustained in the defense of our Constitution the opportunity for optimal recovery and restoration of function

MISSION

Address the most significant gaps in care for the leading burden of injury and loss of fitness for military duty by funding innovative, high-impact, clinically relevant research to advance optimal treatment and rehabilitation from musculoskeletal injuries sustained during combat or combat-related activities

"The Peer Reviewed Orthopaedic Research Program has enabled record levels of research and development to address the most visible and grievous wounds of war. It has also benefited the families who usually bear a great portion of the burden caring for these wounded service members. Almost unrecognized is the impact of this program in advancing the state of medical care for civilians with significant orthopaedic injuries. It is most rewarding to contribute to a program that is making such a difference."

COL Dallas Hack
USAMRMC Combat Casualty Care Research Area Directorate
PRORP Integration Panel Member FY09–FY12

PRORP Research Highlights

Use of Photodynamic Therapy Treatment to Promote Long Bone Fracture Healing

Margarete K. Akens, Dr. med. vet., Ph.D., Sunnybrook Research Institute, Toronto, Canada

Dr. Margarete K. Akens of the Sunnybrook Research Institute in Toronto, Canada, knows that when high-impact trauma is the cause of a long bone fracture, nothing is straightforward. This type of extremity combat injury is usually associated with complications, such as lacerated soft tissue or an open wound, making the wound prone to infections that negatively impact bone healing. Even with the currently available treatments to enhance bone healing, these fractures can take up to a year to fully heal. Dr. Akens' strategy is to improve healing in complex skeletal injuries by using a drug-light therapy method called photodynamic therapy (PDT). In PDT, a photosensitizing drug is locally or intravenously administered and later activated at the site of the fracture with a laser light. One previous study with PDT showed that this approach could rapidly improve vertebral bone strength, stiffness, and architecture while another study showed that PDT could reduce bacterial growth within bone in a preclinical model of infected bone.

With funding from an FY09 Hypothesis Development Award, Dr. Akens has been able to test the treatment in fractured long bones in rats using the photosensitizer, Visudyne®, which is U.S. Food and Drug Administration approved for treating macular degeneration in the eye. Dr. Akens demonstrated an increase in bone and callus formation after PDT treatment with best results when PDT is applied during the secondary stage of fracture healing. She hopes that if ongoing studies confirm the benefits of PDT treatment at the secondary stage of fracture healing, PDT could be applied to trauma patients expected to encounter impaired fracture healing.

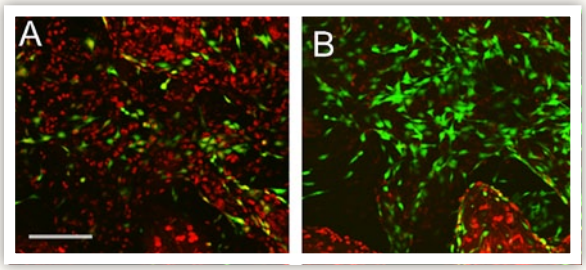
Promoting Cartilage Stem Cell Activity to Improve Recovery from Joint Fracture

James A. Martin, Ph.D., Department of Orthopaedics and Rehabilitation, University of Iowa

Intra-articular fracture (IAF) is a leading cause of post-traumatic osteoarthritis (PTOA), a syndrome characterized by cartilage loss with disabling stiffness and pain. Acute joint injury damages cartilage cells, or chondrocytes, which surgical repair techniques cannot address. The resulting cascade of cell death and inflammation from chondrocyte damage is thought to lead to further cartilage degeneration, accounting for the high risk of developing PTOA after joint fracture. Recent studies have shown that drug treatments to halt cell death can dramatically improve chondrocyte viability after injury. Dr. James A. Martin of the University of Iowa found migratory cells on cartilage surfaces and believes it will be possible to find chemotactic factors to attract these healthy cells and restore the cell population in injured cartilage as an adjunct therapy to current treatments.

With funding from an FY09 Hypothesis Development Award, Dr. Martin demonstrated that the migratory cells found on cartilage surfaces were chondrogenic progenitor cells (CPCs) with stem cell characteristics. Dr. Martin determined that CPCs were highly reactive to alarmins present in chondrocyte lysates, especially the chemoattractant nuclear protein high-mobility group box 1 (HMGB1). CPCs were shown to invade and repopulate cartilage-defective areas in response to substantial chondrocyte death from injury in animal explant studies. Dr. Martin found that CPCs may also have a pathogenic role, however, as they highly express harmful collagenases and other matrix proteases associated with osteoarthritis as well as chemokines that promote inflammation.

Dr. Martin has helped to elucidate an important step of the largely unknown pathogenesis of cartilage degeneration following IAF, opening the doors to better knowledge and possible treatment and prevention of PTOA. Dr. Martin is examining drugs capable of blocking CPC activation to determine if CPCs can be recruited to minimize chondrocyte damage by repopulating and restoring cartilage function without harmful side effects. Such treatments could ultimately facilitate more rapid and complete return to military tasks following joint injuries and substantially improve the quality of life for anyone recovering from IAF.



Confocal micrographs show grafted chondrogenic progenitor cells (green) as they migrate to an injury site on the surface of a cartilage explant. Host chondrocytes are labeled red. The same site was imaged at 3 days after injury (A) and 7 days after injury (B), demonstrating that the numbers of progenitor cells increase over time. Further investigation revealed that the alarmin HMGB1, a protein released from dead chondrocytes, stimulated progenitor chemotaxis. The bar in A indicates 200 microns.

Compliance and Adaptive Underactuation for Prosthetic Terminal Devices

Aaron Dollar, Ph.D., Yale University, New Haven, Connecticut

More than 300,000 people in the United States are currently living with some form of upper limb loss. In addition, approximately 20% of the nearly 40,000 injured service members from the Iraqi and Afghan conflicts have suffered trauma to their upper extremities. These numbers highlight the challenge faced by the medical establishment to provide new and innovative functional interventions that enhance the quality of life of these patients. To date, anyone who has need of an upper limb prosthetic device must balance their preference for esthetics, functionality, durability, and cost. In general, passive devices tend to be more lifelike but provide little to no functionality. On the other hand, the mechanical cable prosthesis with a two-pronged hook, which was invented in the early 20th century, although not esthetically pleasing, remains the most functionally preferred device. In the past several years, there have been great strides in the development of novel prosthetic hands and terminal devices that take advantage of the latest materials and technological advances. A variety of prosthetic terminal devices have appeared on the market designed to perform all kinds of activities from golf, wall climbing, and racquetball to guitar playing and cooking. However, the ultimate goal of a highly functional, durable, and anthropomorphic prosthetic hand, as widely popularized in movies like *Star Wars* and *I, Robot*, remains confined to the realm of science fiction.

In FY09, Dr. Aaron Dollar was granted a Hypothesis Development Award to develop an anthropomorphic, body-powered prosthetic hand prototype that is mechanically compliant and passively adaptive. Although body-powered anthropomorphic hands have been developed in the past, the new design achieves mechanical compliance through the distribution of force from a single body-powered cable input to the five fingers. In addition, polymer-based flexion joints actively bend, allowing for passive deflection of the fingers during contact with an object, as well as keeping contact forces low during object acquisition. Another aspect of this novel prototype is that the thumb can be rotated to a number of different positions, permitting the hand to accomplish a larger range of grasps, thereby greatly improving the practical use of this terminal device. Laboratory testing of the hand has already proven the functionality of this device in achieving a range of grasping positions as well as various areas for improvement. Dr. Dollar's future work will focus on developing an actuated wrist to accompany the hand and conducting clinical trials in upper limb amputees to evaluate the device's real-world performance, and in doing so, bring the world of fantasy and science fiction within grasp.

Hasten Physical Therapy Access for Better Treatment of Lower Back Pain

MAJ Daniel Rhon, PT, DPT, DSc, OCS, FAAOMPT, Madigan Army Medical Center, Tacoma, Washington

Low back pain (LBP) is one of the largest causes of attrition for Soldiers in combat; it is the most frequent reason for non-battle injury evacuations and is associated with one of the lowest return-to-combat rates. LBP is not only associated with direct costs, such as health care services and prescription medication, but also with significant indirect costs, such as lost work productivity, long-term disability, pensions, and Department of Veterans Affairs-related ongoing care. During combat deployment, MAJ Daniel Rhon of the Madigan Army Medical Center witnessed firsthand the impact of LBP on deployed Soldiers and recognized the need for studies to determine which treatment methods are the most effective in treating the condition. Previous studies have validated the benefit of appropriate early physical therapy (PT) for other musculoskeletal conditions. MAJ Rhon believes that earlier access to PT along with implementation of a treatment-based classification (TBC) algorithm will provide greater improvements in function and quality of life and decreased health care utilization as compared to the usual "stepped" care approach and that these improvements will be sustained to at least 1 year.

With funding from an FY10 Career Development Award and under the mentorship of Dr. Julie Fritz at the University of Utah, MAJ Rhon is conducting a clinical trial to determine exactly which treatment type will best benefit Brigade Combat Team Soldiers with recent onset of LBP. Both treatment groups will receive advice and education for 4 weeks. The usual care group will be managed by a standard stepped-care approach that typically lacks early referral to PT. The PT group will receive up to eight PT sessions guided by a TBC algorithm during those 4 weeks. Differences in health care utilization and psychosocial factors between the two groups will be compared 1, 3, and 12 months after the study begins. MAJ Rhon hopes that by validating the benefits of earlier PT, overall treatment costs for Soldiers with combat-related LBP in the long term can be significantly reduced, and their quality of life can be significantly increased.

Engineered PlyCB for the Treatment of Orthopaedic Injuries in the Wounded Warrior

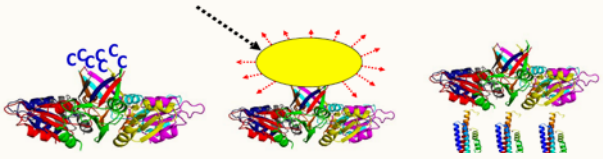
Daniel Nelson Ph.D., University of Maryland

More than 65% of all injuries suffered by casualties in the current conflicts in Iraq and Afghanistan are orthopaedic in nature. Some of the major challenges in treating upper and lower extremity injuries include infection of the bone (osteomyelitis) and the integration between the healing bone and orthopaedic implants (osseointegration). Many strains of bacteria are highly resistant to antibiotic drugs, and infections are becoming increasingly difficult to treat. Moreover, currently available orthopaedic implant materials are incompatible with osteoblasts and often do not integrate with the healing bone, leading to implant failure.

To address these challenges, Dr. Daniel Nelson, a recipient of two FY09 Hypothesis Development Awards, is utilizing a bacteriophage-derived lysin called PlyCB as a platform. Bacteriophages are viruses that prey on bacteria and produce enzymes called lysins to break down their hosts' cellular wall. Previously, Dr. Nelson purified PlyCB from the streptococcal bacteriophage C1, which self-assembles into a highly stable octamer. Some of PlyCB's unique features include its high resistance to heat and chemicals, its ability to bind specifically to *Streptococcus* bacteria, and its high affinity for hydroxyapatite (HA) and tricalcium phosphate (PTC), materials that are often used to coat orthopaedic implants. Additionally, PlyCB can be genetically engineered to display any number of bioactive peptides or proteins without losing these properties.

With PRORP support, Dr. Nelson developed customized PlyCB to tackle both osteomyelitis and osseointegration. To address osteomyelitis, Dr. Nelson aimed to develop gold nanoparticles that specifically home to the surface of bacteria and produce intense local heat when exposed to infrared radiation (IR), killing only the target cells while sparing healthy cells. In proof-of-principle experiments, Dr. Nelson constructed PlyCB/gold nanoparticle complexes, which successfully achieved streptococcal-specific binding and thermal ablation in vitro. Additionally, Dr. Nelson produced PlyCB fused with a pneumococcal binding domain, demonstrating that PlyCB's binding specificity may be altered as needed. To address challenges in osseointegration, he sought to develop synthetic bone scaffolds that can actively recruit osteoblasts to the implant surface to promote bone differentiation and osseointegration. In addition, Dr. Nelson evaluated whether PlyCB can be engineered to display bioactive peptides (e.g., RGD) that recruit osteoblasts while bound to HA and TPC. Several versions of PlyCB-RGDs were engineered, all of which retained their stability and high affinity for HA and TPC. Importantly, Dr. Nelson demonstrated direct binding between PlyCB-RGD and osteoblasts in vitro.

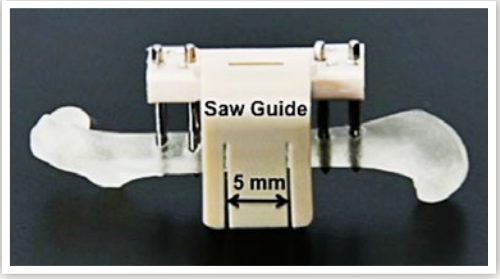
While the development of PlyCB for therapeutic applications is still in its initial stages, these results showcase PlyCB's versatility and potential for addressing important issues in treating upper and lower extremity injuries. The success of these studies may lead to significant advancements in treating antibiotic-resistant infections and improve the outcome of those receiving orthopaedic implants.



Left, PlyCB N-terminus functionalized with cysteine residues for attachment to nanoparticles. Center, principle of thermal ablation. Infrared radiation (black arrow) causes heating (red arrows) of nanoparticles complexed to PlyCB, which bind tightly to the streptococcal surface, thus killing the bacteria by thermal ablation. Right, engineering the PlyCB C-terminus with other cell wall binding domains to target additional bacterial pathogens of interest.

Enhanced Healing of Segmental Bone Defects by Modulation of the Mechanical Environment

Christopher Evans, Ph.D., Beth Israel Deaconess Medical Center



Military service members deployed to Iraq and Afghanistan frequently suffer from blast-related injuries, including the loss of large sections of bone (segmental bone defects) and severe soft tissue damage. Segmental bone defects often fail to heal due to the size of the lost bone piece and the extent of damage to surrounding soft tissue. Failure of these large segmental bone defects to heal can result in severe deformity and/or amputation. Although mechanical stabilization through nailing and plating increases the rate of bone fracture healing, the effect of mechanical stabilization on large segmental bone defects is not well understood. Dr. Christopher Evans, with funding from an FY09 Idea Development Award, is investigating the effect of mechanical manipulation on the healing of large segmental bone defects in an animal model. Dr. Evans' research team has developed an external fixator that fits onto the thigh bones of rats with large segmental bone defects. The stiffness/stabilization level of the novel fixator can be modulated by a connection element that is secured to the rat femur with titanium screws. In a preliminary study, the degree of stiffness of the fixators was either maintained at a constant level or increased through the different stages of bone healing. Interestingly, it was demonstrated that stiffness modulation significantly accelerated large segmental bone healing, suggesting that troops suffering from blast-related segmental bone defects may benefit from this technique.

The Vision for FY12

The PRORP challenges the scientific community to design innovative research that will foster new directions for and address neglected issues in orthopaedic research and the treatment of combat-relevant orthopaedic injuries. In FY12, Congress continued the PRORP with an appropriation of $30M. The following three award mechanisms addressing underfunded priorities were offered.

Focus	Award Mechanism
 Clinical Research	**Clinical Trial Award:** Supports the rapid implementation of clinical trials with the potential to have a significant impact on military combat-relevant orthopaedic injuries. Trials may evaluate promising new products, pharmacologic agents (drugs or biologics), devices, clinical guidance, and/or emerging approaches and technologies.
 Partnership	**Translational Research Partnership Award:** Supports translational research with the potential to benefit Warfighters with combat-relevant traumatic orthopaedic injuries. Supports multidisciplinary research partnerships among two or three investigators to accelerate the movement of promising research hypotheses into clinical application in a manner that would be less readily achievable through separate efforts.
 Innovative Research	**Idea Development Award:** Promotes new ideas that are in the early stages of development and have the potential to yield highly impactful data and new avenues of investigation. Supports conceptually innovative, high-risk/potentially high-reward research that could ultimately lead to critical discoveries or major advancements in the clinical care of combat-related orthopaedic injuries.

Each award mechanism required applicants to address a subset of the FY12 focus areas:

- Treatment and prevention of heterotopic ossification
- Prevention or treatment of post-traumatic joint stiffness and contracture in the ankle, knee, and/or elbow
- Short-term and long-term outcomes in limb salvage populations
- Improvement of moisture management and residual limb skin care at the prosthetic socket interface
- Improvement of the rate of nerve regeneration
- Strategies to inhibit neuromas at surgical/amputation sites
- Mitigation of the musculoskeletal and physiologic effects of reduced mobility for polytrauma patients
- Treatment of segmental bone injury or loss in weight-bearing locations
- The comparative effectiveness of local strategies to minimize surgical site infection

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