



# FY16

Science & Technology Efforts & Programs

## PREVENTION, MITIGATION, AND TREATMENT OF BLAST INJURIES

REPORT TO THE EXECUTIVE AGENT





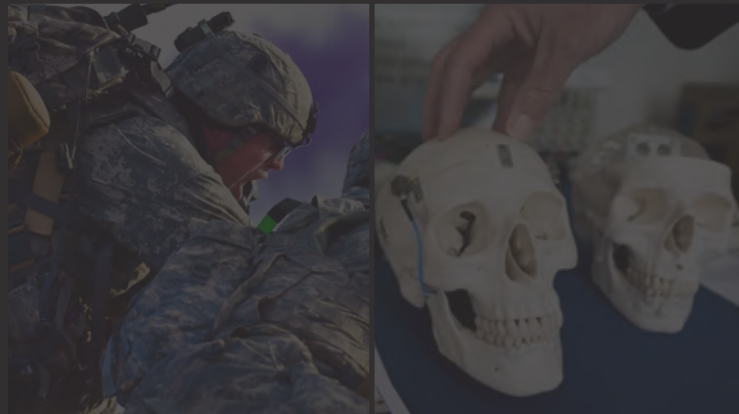
# TABLE OF CONTENTS

Foreword from the Director .....	1
Acknowledgments .....	3
Executive Summary .....	4
Chapter 1: Introduction.....	10
Chapter 2: DoD Blast Injury Research Program Coordinating Office .....	20
Chapter 3: NATO Human Factors and Medicine Research Task Group .....	38
Chapter 4: MHS Blast Injury Prevention Standards Recommendation Process.....	44
Chapter 5: Blast-related Traumatic Brain Injury .....	56
Chapter 6: Warrior Injury Assessment Manikin.....	70
Chapter 7: DoD Blast Injury Research Program Accomplishments .....	90
Chapter 8: Way Forward .....	192
Appendix A: Acronyms.....	204
Appendix B: References .....	212
Appendix C: DoDD 6025.21E.....	226
Appendix D: Supplemental Tables .....	234

Cover photo credit: SrA Chris Willis/US Air Force

Photo credits for this page, top to bottom:

1. Ilka Cole/US Air Force
2. Justin Connaher/US Air Force
3. Department of Defense
4. Cpl Devan K. Gowans/US Marine Corps
5. SSgt Christopher Boitz/US Air Force





# FOREWORD FROM THE DIRECTOR

---



Photo credit: EJ Hersom/DoD

United States Air Force Master Sergeants (MSgt) Kyle Burnett and Reese Hines have another title in common—Ultimate Champion. Both earned the title in the United States Department of Defense (DoD) Warrior Games, during which wounded, ill, and injured Service Members and Veterans compete in individual and team events. To earn the prestigious title of Ultimate Champion, athletes must achieve the highest individual score after competing in five events within their respective disability classification. MSgt Burnett, a computer networks operations technician, won the title of Ultimate Champion in the 2015 Warrior Games after she suffered a traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) following a rocket attack while serving in Iraq in 2009. Inspired by her win, MSgt

Hines competed for the first time in 2016 and won the title himself. MSgt Hines is an explosive ordinance disposal technician who was two feet away from a remotely detonated improvised explosive device while serving in Afghanistan in 2011. MSgt Hines suffered a TBI (including a bolt in his skull), damage to both eyes (resulting in the removal of one eye), severe damage to his right hand, a broken jaw, ruptured eardrums, soft tissue damage, nerve damage, and PTSD. Learning to overcome the challenges of their traumatic injuries, MSgt Burnett, MSgt Hines, and all the Service Members and Veterans who participate in the Warrior Games bring their bravery, perseverance, and resolve to the athletic arena. These athletes not only inspire others with their determination and individual accomplishments, but they also build lifelong bonds with fellow athletes and support each other's journey through recovery.<sup>1</sup>

The DoD Blast Injury Research Program and the Program Coordinating Office (PCO) work diligently to guide research to improve mechanisms to better protect, treat, and support the rehabilitation of Service Members like MSgt Burnett and MSgt Hines who have been injured by blasts and explosions. The development of life-saving protective technology begins with collaborative medical and nonmedical research on traumatic events and their injurious consequences. The collective efforts of multidisciplinary researchers in the DoD Blast Injury Research Program combine knowledge of blast events, mechanism of injury, and product performance to develop new strategies that protect the Service Member in training and in combat, whether mounted or on foot. Scientists and clinicians are also making notable advances in treatment and rehabilitation to save lives, reduce injury, and speed the



recovery and reintegration of Service Members into their military roles and civilian lives. The DoD Blast Injury Research Program and the PCO play a critical role in supporting the Service Member by facilitating collaboration across the research, development, test and evaluation communities; disseminating blast injury research information; identifying blast injury knowledge gaps; and shaping medical research programs to fill identified gaps.

This annual report to the Executive Agent (EA) describes the DoD Blast Injury Research Program's fiscal year 2016 efforts to address the entire spectrum of blast injuries. It highlights significant accomplishments, explores the remaining challenges, and makes recommendations for advancing the state of the science. By disseminating information on the DoD Blast Injury Research Program to researchers, policymakers, military leaders, and the general public, we hope to demonstrate the power of collaboration and the breadth of partnerships within the diverse blast injury research community. We also want to build confidence in the DoD's commitment to preventing, mitigating, and treating the full range of blast injuries, including the long-term consequences on quality of life and return to duty.

I am pleased to present this report to the EA on behalf of the vast network of dedicated professionals who are the foundation of this program.

**Michael J. Leggieri, Jr.**

Director, DoD Blast Injury Research Program Coordinating Office



# ACKNOWLEDGMENTS

---

The Department of Defense (DoD) Blast Injury Research Program Coordinating Office is enormously grateful to the many individuals and organizations across the DoD who contributed to this report and the work it summarizes. Particular recognition goes to the collaborative science and technology efforts that are leading the way toward improved strategies for the prevention, mitigation, and treatment of blast injuries. The dedication of the scientists, clinicians, engineers, and operators who support DoD blast injury research represent a commitment to the health and well-being of Service Members and their Families. In addition, we would like to thank the reviewers for their valuable insights and feedback.

The views expressed in this report are those of the author(s) and do not reflect official policy or position of the Department of the Army, DoD, or the United States (US) Government.

Photo credits, top to bottom: SSgt Sarah Stegman/US Air Force; MSgt Cohen A. Young/US Air Force; Sean Kimmons/US Air Force







# EXECUTIVE SUMMARY



**B**last-related injury has become increasingly common in recent conflicts, including Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn. Improvised explosive devices (IEDs) remain the weapon of choice for militant groups worldwide, with resulting civilian and military injuries spanning the spectrum from mild to severe, including hearing loss, penetrating injuries, burns, fractures and traumatic amputations, and open and closed head injuries. While technological advancements are improving survivability, Service Members are surviving blast events with blast injuries ranging from hearing loss to amputation to traumatic brain injury (TBI). Even relatively mild symptoms of blast injuries (e.g., tinnitus, dizziness, disorientation) can have major effects on operational readiness and quality of life. To address these effects, the United States (US) Department of Defense (DoD) is investing significant resources in medical and nonmedical research on the prevention, mitigation, and treatment of blast injuries.

In Section 256 of Public Law 109-163, National Defense Authorization Act for fiscal year 2006 (FY06), Congress directed the Office of the Secretary of Defense (OSD) to designate an Executive Agent (EA) to coordinate DoD medical research efforts and programs relating to the prevention, mitigation, and treatment of blast injuries. DoD Directive (DoDD) 6025.21E formalized the DoD's blast injury research efforts. This directive established the DoD Blast Injury Research Program and assigned EA responsibilities to the Secretary of the Army. These responsibilities include recommending DoD blast injury prevention and treatment standards, ensuring DoD-sponsored blast injury research programs address the Services' needs, and sharing blast injury research information among medical and nonmedical communities.

Following a series of delegations, the Commander, US Army Medical Command

assumed EA authority for the DoD Blast Injury Research Program and established the Program Coordinating Office (PCO) at the US Army Medical Research and Materiel Command to assist in fulfilling EA responsibilities and functions. The PCO coordinates the DoD's blast injury research on behalf of the EA to ensure that critical knowledge gaps are addressed, avoid costly and unnecessary duplication of effort, and accelerate the fielding of prevention and treatment strategies through collaboration and information sharing.

This report highlights the PCO's FY16 activities that support the congressional intent for a coordinated DoD blast injury research program. Over the past year, the PCO completed the deliverables for the North Atlantic Treaty Organization (NATO) Human Factors and Medicine (HFM) Research Task Group (RTG) on "Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards" (HFM-234); started planning for the new NATO HFM-270 (RTG) on the "Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-Related Threats"; directed the Military Health System (MHS) Blast Injury Prevention Standards Recommendation (BIPSR) Process; sponsored the fifth annual International State-of-the-Science (SoS) Meeting on the question, "Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?"; and planned the sixth annual International SoS Meeting on Minimizing the Impact of Wound Infections Following Blast-Related Injuries.

In accordance with DoDD 6025.21E, the PCO fosters international collaboration to support the prevention, mitigation, and treatment of blast injuries. The PCO Director chaired the NATO HFM-234 (RTG), which includes 17 members representing nine NATO nations. Its objective is to develop tools that will guide current and future blast injury research efforts in support of the Service

Member. The task group has developed a comprehensive dictionary of blast injury research terms to facilitate communication and collaboration across research and operational communities, as well as guidance documents for conducting blast injury epidemiological studies, reproducing relevant blast exposure conditions in the laboratory, and using animal models in blast injury research. These guidance documents will promote standardized study and data collection methodologies, facilitate cross-study comparisons, and advance the state of the science.

The EA is responsible for recommending blast injury prevention standards to the Assistant Secretary of Defense for Health Affairs, who approves them as DoD standards. To support this key EA responsibility, the PCO developed the BIPSR Process—the DoD’s first unbiased, stakeholder-driven critical assessment methodology for recommending biomedically valid blast injury prevention standards. These standards support weapon system health hazard assessments, combat platform occupant survivability assessments, and protection system development and performance testing. In FY16, the BIPSR Process for the Spine and Back and Upper Extremity Blast Injury Types were completed; progress was also made in analyzing standards for preventing auditory injuries. The PCO also continued to prove out the new, streamlined BIPSR Process through a web-based collaboration environment, known as Interactive Blast Injury Prevention Standards Recommendation using the Auditory Blast Injury Type as an exemplar. In addition, the PCO initiated a reprioritization effort for the remaining MHS BIPSR Process Blast Injury Types to ensure that the current needs of the operational environment and DoD are being met.

The EA identifies blast injury knowledge gaps and facilitates collaboration among the world’s blast injury research experts. These two roles help shape medical research programs that can in turn address the gaps and meet the needs of the Services.

To support these EA responsibilities, the PCO established the International SoS Meeting Series to address specific blast injury issues important to the DoD. These annual working meetings composed of subject matter experts and stakeholders, explore the state-of-the-science for specific blast injury challenges, and identify gaps to guide future medical research. In FY16, the PCO sponsored the fifth International SoS Meeting addressing the question, “Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?” and planned the sixth International SoS Meeting on Minimizing the Impact of Wound Infections Following Blast-Related Injuries. Meeting materials are posted to the PCO website (<https://blastinjuryresearch.amedd.army.mil>).

Two chapters of this report highlight the programs and efforts of two key stakeholders in the field of blast injury research, development, and clinical care: the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) and the Warrior Injury Assessment Manikin (WIAMan) project. The DCoE provides the MHS with current and emerging psychological health and TBI clinical and educational information; identifies and prioritizes gaps in psychological health and TBI research; and translates research into clinical practice to improve patient outcomes. The WIAMan project investigates human response and tolerance to vertical accelerative loads that can produce tertiary blast injuries, and uses that knowledge to create a scientifically valid test capability for evaluating the survivability of Service Members in ground vehicles hit by IEDs that can be used in research, development, and acquisition.

The research accomplishments, initiatives, and activities highlighted in this FY16 annual report reflect the extent of collaboration within the blast injury research community. This report details 140 accomplishments that extend the knowledge base for blast injury research and establish new tools and strategies for preventing,





Photo credit: SGT Anthony Hewitt/US Army

mitigating, and treating blast injuries. These accomplishments were sourced from 32 DoD organizations and partners representing the research, development, test, and evaluation communities as well as the operational and clinical care communities.

For example, the Surgical Critical Care Initiative (SC2i) at the Uniformed Services University of the Health Sciences developed a clinical decision support tool (CDST) that can predict those combat trauma patients at the highest risk for developing venous thromboembolism (VTE); rates of VTE in the combat wounded can reach up to 28 percent and complications are severe, including death. This

CDST guides medical professionals to accurately apply resources for VTE screening and prophylaxis in at risk combat trauma patients. SC2i has developed several other CDSTs including: the WoundDx CDST which assists surgeons in determining the optimal timing of traumatic wound closure thereby decreasing the time from injury to successful wound closure; the massive transfusion protocol which allows for the accurate prediction of who may require a massive transfusion; and the invasive fungal wound infections (IFI) CDST for early diagnosis of patients with or at risk of IFI, enabling early or prophylactic treatment thus reducing mortality and morbidity.

In another example, the Office of Naval Research supported the development and optimization of low-cost helmet coatings. These coatings enhance the helmet's protection against mild TBI, ballistic, sharp-edged flechette-type devices, and weight requirements. The polymer coated helmet exceeds military standards (MIL-STDs) for ballistic protection, while satisfying all other MIL-STDs.

Supported by the Clinical and Rehabilitative Medicine and Reconstructive Transplant Research Programs, researchers from the New York University School of Medicine developed a novel paradigm in surgical technology to facilitate precision during two major phases of a vascularized composite allotransplantation (VCA) procedure – recipient preparation and donor procurement. This paradigm reduces the time required for donor procurement, recipient preparation, transplantation of the donor allograft, and the total operative time to complete the transplant, by 49-60 percent; thus improving the reconstruction of devastating craniofacial injuries by providing a standardized and custom VCA surgical process which is defined by both the donor and recipient anatomies.

Funded by the Navy Bureau of Medicine Wounded, Ill, and Injured Program, researchers at Naval Health Research Center and Department of Veterans Affairs (VA) at the VA San Diego Healthcare System, found that lower limb amputation, and particularly bilateral lower limb amputation, is associated with increased cardiovascular disease risk. The study identifies an important modifiable variable, namely bodyweight or body mass index, which is associated with increased

likelihood of metabolic syndrome for patients with lower limb amputations. The results support the need for primary care and lifestyle interventions to manage weight and lipid levels, particularly following combat-related amputations.

Researchers at the University of Dallas, Texas, initially funded by the Defense Medical Research and Development Program and continued under the Joint Warfighter Medical Research Program tested the Strategic Memory and Reasoning Training (SMART) program for its effectiveness to improve strategic attention, higher-order reasoning, and innovative problem solving to help Service Members return to a productive work life after injury. The researchers demonstrated that the SMART program led to gains in cognitive functioning, reduced symptoms of depression, as well as changes in cerebral blood flow and measures of white matter integrity suggesting that this program has the ability to improve cognitive capacity and enhance brain function in Service Members through the use of a manualized, evidence-based higher-order cognitive training protocol.

These and other accomplishments submitted to the PCO for inclusion in this report represent a significant body of work in the field and should inspire confidence among Service Members, their Families, and the general public—major advances are helping to protect Service Members from blast injuries and those injured throughout their treatment and recovery.







01



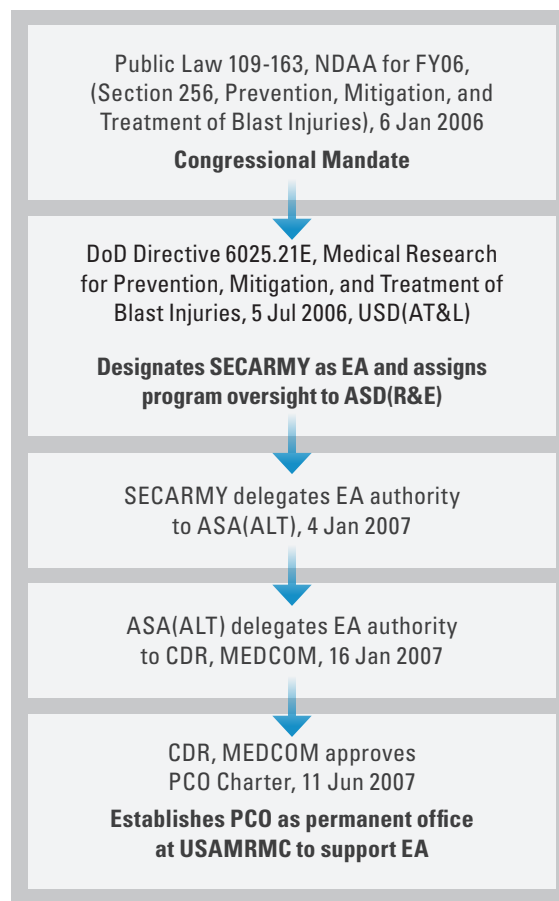
CHAPTER 1:  
**INTRODUCTION**

**T**errorist and insurgent activities worldwide necessitate a focus on blast injury research and the sharing of knowledge between the civilian and military sectors. Improvised explosive devices (IEDs) remain the weapon of choice for militant groups worldwide, with resulting civilian and military injuries spanning the spectrum from mild to severe, including hearing loss, penetrating injuries, burns, fractures and traumatic amputations, and open and closed head injuries. Data from 2008 indicate blasts were responsible for approximately 75 percent of US combat casualties in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).<sup>2</sup> Blast injuries continue to be a concern in the current Operation Freedom’s Sentinel—between June 2014 and May 2016, the number of IED or mine attacks in Afghanistan ranged between 200 and 400 per month.<sup>3</sup> Civilians are also affected by the prolific use of explosive devices, which killed almost 200 in recent attacks in Turkey, 32 in Brussels, and three (plus 264 wounded) in the 2013 Boston Marathon bombing.

The impact of explosive devices on United States (US) military operations, Service Members and their Families, and civilian victims of conflict and terrorism, emphasize the need for coordinated research investments on the prevention, treatment, and rehabilitation of blast injuries. In 2006, Congress passed legislation to address critical gaps associated with blast injury research. In Section 256 of Public Law 109-163, National Defense Authorization Act (NDAA) for fiscal year 2006 (FY06), Congress directed the Office of the Secretary of Defense (OSD) to designate an Executive Agent (EA) to coordinate Department of Defense (DoD) medical research efforts and programs relating to the prevention, mitigation, and treatment of blast injuries. In response to this direction, Department of Defense Directive (DoDD) 6025.21E, Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, formally established the DoD Blast Injury Research Program on 5 July 2006 (see Appendix C: DoDD 6025.21E).

DoDD 6025.21E assigned the Assistant

**FIGURE 1-1: Assignment of EA Authority\***



\* USD(AT&L)=Under Secretary of Defense for Acquisition, Technology, and Logistics.

Secretary of Defense for Research and Engineering (ASD(R&E)) with oversight of the Blast Injury Research Program and designated the Secretary of the Army (SECARMY) as the DoD EA (Figure 1-1).

The SECARMY delegated authority and assigned responsibility to execute EA responsibilities to the Assistant Secretary of the Army for Acquisition, Logistics, and Technology (ASA(ALT)). The ASA(ALT) further delegated authority and assigned program responsibility to the Commander, US Army Medical Command (MEDCOM). The Blast Injury Research Program Coordinating Office (PCO) was established within MEDCOM at the US Army Medical Research and Materiel Command (USAMRMC), Fort Detrick, Maryland, to assist the Commander, MEDCOM, in fulfilling the EA’s assigned responsibilities and functions.



To support the EA, the PCO coordinates relevant DoD medical research efforts and programs. Its role includes facilitating collaboration, identifying blast injury knowledge gaps, shaping medical research programs to fill identified gaps, disseminating blast injury research information, and promoting information sharing among DoD and non-DoD entities (Figure 1-2). Through these efforts, the PCO works to improve blast injury prevention, mitigation, and treatment strategies for Service Members and their Families.

## Responsibilities and Functions

DoDD 6025.21E assigned key DoD components with specific responsibilities to coordinate and manage the medical research efforts and DoD programs related to the prevention, mitigation, and treatment of blast injuries. The following is a summary of the responsibilities assigned by the Directive. For a more detailed description, please see Appendix C: DoDD 6025.21E.

- **The ASD(R&E)** establishes procedures to ensure new technology developed under the DoDD is effectively transitioned and integrated into systems and transferred to DoD components; chairs the Armed Services Biomedical Research, Evaluation and Management (ASBREM) Community of Interest (COI); oversees the functions of the DoD EA; and serves as the final approving authority for DoD blast injury research programs.
- **The Assistant Secretary of Defense for Health Affairs (ASD(HA))** assists in requirements development; assesses and coordinates relevant research efforts to resolve capability gaps; approves Military Health System (MHS) blast injury prevention, mitigation, and treatment standards; appoints representatives to DoD EA coordination boards and committees; and ensures the information systems capabilities of the MHS support the EA.
- **The SECARMY** was designated as the DoD EA for Medical Research for Prevention,

Mitigation, and Treatment of Blast Injuries. In 2007, the SECARMY delegated authority and assigned EA responsibility to ASA(ALT). ASA(ALT), delegated authority and assigned responsibility to the Commander, MEDCOM.

- **The Commander, MEDCOM**, as the delegated EA, coordinates and manages DoD blast injury research efforts and programs by:
  - Maintaining a DoD technology base for medical research related to blast injuries
  - Performing programming and budgeting actions for all blast injury research based on analysis and prioritization of DoD component needs
  - Providing medical recommendations on Military Health System blast injury prevention, mitigation, and treatment standards
  - Executing the approved DoD Blast Injury Research Program
  - Ensuring that blast injury research information is shared.
- **The Secretary of the Navy and the Secretary of the Air Force** assist in requirements development and coordinate all blast injury research efforts and requirements throughout the EA.
- **The President of the Uniformed Services University of the Health Sciences (USUHS)** ensures education relating to blast injury prevention, mitigation, and treatment is included in the USUHS medical education curriculum and programs. The president coordinates all blast injury research efforts and requirements through the EA, and appoints representatives to any coordination boards or committees related to blast injury research.
- **The Chairman of the Joint Chiefs of Staff (CJCS)** coordinates all blast injury efforts and requirements through the EA; appoints a senior member to the ASBREM COI; and appoints representatives to any coordination boards or committees related to blast injury research.



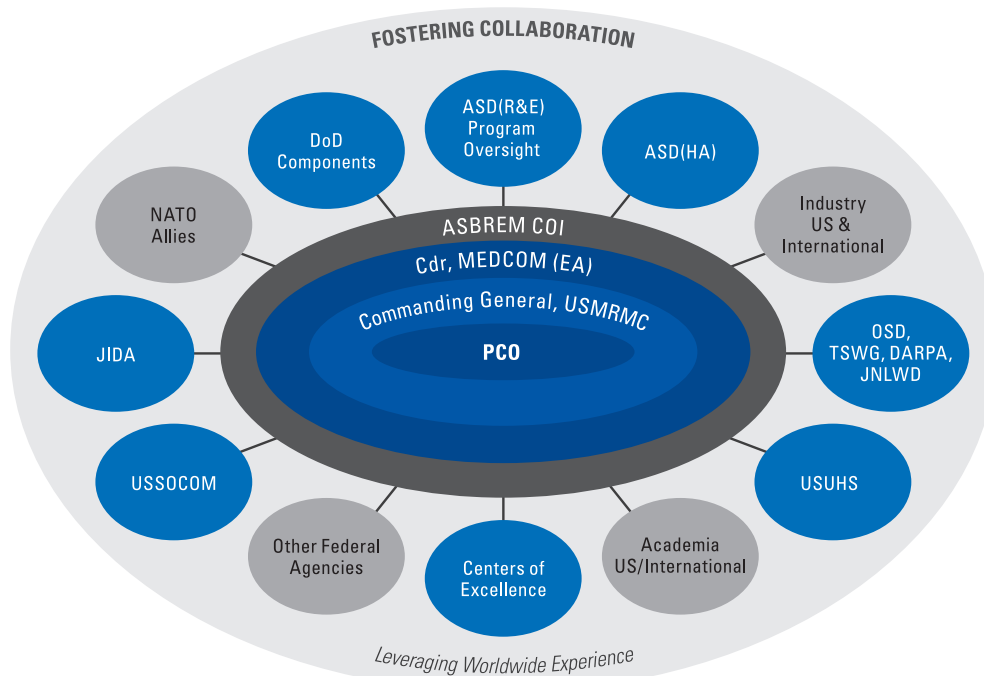
- **The Commander, US Special Operations Command (USSOCOM)** establishes procedures for the coordination of Defense Major Force Program II activities with those of the EA; forwards the Command’s approved blast injury research requirements to the DoD EA; and appoints representatives to the ASBREM COI and any other coordination boards or committees related to blast injury research.
- **The Joint Improvised Explosive Device Defeat Organization (JIEDDO), now known as the Joint Improvised-Threat Defeat Agency (JIDA),** supported the development, maintenance, and usage of a joint database on the efficacy of in theater Personal Protective Equipment (PPE) and vehicular equipment designed to protect against blast injury by helping to establish the Joint Trauma Analysis and Prevention of Injuries in Combat (JTAPIC) Program. The JTAPIC Program fulfills the intent of a “joint database” by providing a process that enables data sharing and analysis across communities. Continuing responsibilities

include identifying related operational and research needs, coordinating research efforts to resolve capability gaps, and appointing representatives to the ASBREM COI and any other coordination boards or committees related to blast injury research.

### DoD Framework for Characterizing Blast Injuries






The EA plays a key role in coordinating research and development for the entire spectrum of blast injury that can result from exposure to explosive weapons, ranging from hearing loss, penetrating injuries, burns, fractures and traumatic amputations, and open and closed head injuries. The DoD adopted the *Taxonomy of Injuries from Explosive Devices*, as defined in DoDD 6025.21E, to provide a common framework for characterizing the full spectrum of blast injuries. The *Taxonomy of Injuries from Explosive Devices* assigns blast injuries to five categories—Primary, Secondary, Tertiary, Quaternary, and Quinary—based on the mechanism of injury (see Table 1-1).

**FIGURE 1-2: Breadth of the PCO’s Coordinating Responsibilities**



Joint Improvised-Threat Defeat Agency (JIDA); Joint Non-Lethal Weapons Directorate (JNLWD); Technical Support Working Group (TSWG); North Atlantic Treaty Organization (NATO)

**TABLE 1-1: Taxonomy of Injuries from Explosive Devices**

Injury Type	Description	
<p><b>Primary Blast Injuries:</b></p> <ul style="list-style-type: none"> <li>• Blast lung</li> <li>• Ear drum rupture and middle ear damage</li> <li>• Abdominal hemorrhage and perforation</li> <li>• Eye rupture</li> <li>• Non-impact induced mild traumatic brain injury</li> </ul>	<p>Primary blast injuries result from the high pressures created by the blast. These high pressures, known as blast overpressure, can crush the body and cause internal injuries. Primary blast injuries are the only category of blast injuries that are unique to blast.</p>	
<p><b>Secondary Blast Injuries:</b></p> <ul style="list-style-type: none"> <li>• Penetrating ballistic (fragmentation or blunt injuries)</li> <li>• Eye penetration</li> </ul>	<p>Secondary blast injuries result when strong blast winds behind the pressure front propel fragments and debris against the body and cause blunt force and penetrating injuries.</p>	
<p><b>Tertiary Blast Injuries:</b></p> <ul style="list-style-type: none"> <li>• Fracture and traumatic amputation</li> <li>• Closed and open brain injury</li> <li>• Blunt injuries</li> <li>• Crush injuries</li> </ul>	<p>Tertiary blast injuries result from strong winds and pressure gradients that can accelerate the body and cause the same types of blunt force injuries that would occur in a car crash, fall, or building collapse.</p>	
<p><b>Quaternary Blast Injuries:</b></p> <ul style="list-style-type: none"> <li>• Burns</li> <li>• Injury or incapacitation from inhaled toxic fire gases</li> </ul>	<p>Quaternary blast injuries are the result of other explosive products (such as heat and light) and exposure to toxic substances from fuels, metals, and gases that can cause burns, blindness, and inhalation injuries.</p>	
<p><b>Quinary Blast Injuries:</b></p> <ul style="list-style-type: none"> <li>• Illnesses, injuries, or disease caused by chemical, biological, or radiological substances</li> </ul>	<p>Quinary blast injuries refer to the clinical consequences of “post-detonation environmental contaminants,” including chemical, biological, and radiological (e.g., dirty bombs) substances.</p>	

from DoDD 6025.21E

## Blast Injury Research Program Areas

The DoD Blast Injury Research Program works to close knowledge gaps in the prevention, mitigation, and treatment of blast injuries. To address the gaps and capability requirements for the full spectrum of blast injuries, the program organizes current research efforts into three key research program areas: Injury Prevention, Acute Treatment, and Reset (see Figure 1-3).

### Injury Prevention

Injury prevention reduces the risk of blast injuries. This research program area provides medically-based design guidelines and performance standards for individual and combat platform occupant protection systems; comprehensive injury surveillance systems that link injury, operational, and protection system performance data; tools to identify individual susceptibility to injury; and individual resilience training to prevent or mitigate injuries.

### Acute Treatment

Research in the area of acute treatment is intended to improve survivability and mitigate long-term disability for Service Members suffering from the full spectrum of injuries following blast events. The acute treatment research program area explores development of new diagnostic tools, interventions for hemorrhage control and resuscitation, strategies to mitigate wound infection, and tools and guidelines for eye injuries. This research program area will lead to a greater understanding of the capabilities and limitations of current technologies; new tools and validated methods for injury mitigation in the prehospital setting; and improved diagnostics and clinical guidelines for the acute treatment of blast injuries.

**FIGURE 1-3: Blast Injury Research Program Areas**



Photo credits: Column 1—US Marine Corps, US Naval Research Laboratory, US Army; Column 2—US Army Medical Command, US Army Medical Research and Materiel Command, US Army; Column 3—US Air Force, Defense Advanced Research Projects Agency, Defense Centers of Excellence.

## Reset

Reset mitigates disability by providing a biomedically-based performance assessment capability for return to duty (RTD) and redeployment following injury; restoring full performance capabilities in redeployed individuals; and restoring function and ability to seriously injured Service Members with prosthetic devices. The term “reset” acknowledges a concept that extends beyond rehabilitation to include all activities necessary to return injured Service Members to duty or to productive civilian lives.

## Coordination of Blast Injury Research Activities

DoD blast injury research efforts are requirements driven and fill knowledge gaps in preventing and treating injury, as well as restoring function. To address these gaps, researchers work with stakeholders from across the blast injury research community. Examples of programs and collaborative efforts supporting blast injury research are discussed below.

## DoD Component Services and Agency Research Programs

Each of the Services and the Defense Advanced Research Projects Agency (DARPA) has blast injury research programs primarily funded through the President’s Budget. These programs sponsor research internally, within DoD laboratories and clinical centers, and externally through academic and industry partnerships. DoD blast injury research focus areas include injury surveillance, combat casualty care (CCC), wound infections, military operational medicine (MOM), and clinical and rehabilitative medicine.

## Defense Health Agency Research and Development (DHA R&D) Directorate

Established in FY10 by the Office of ASD(HA), the DHA R&D Directorate supports medical research, development, testing, and evaluation (RDT&E) programs related to the healthcare needs of Service Members. The DHA R&D Directorate manages the RDT&E funds of the Defense Health Program (DHP). Joint Program Committees (JPC), which consist of DoD

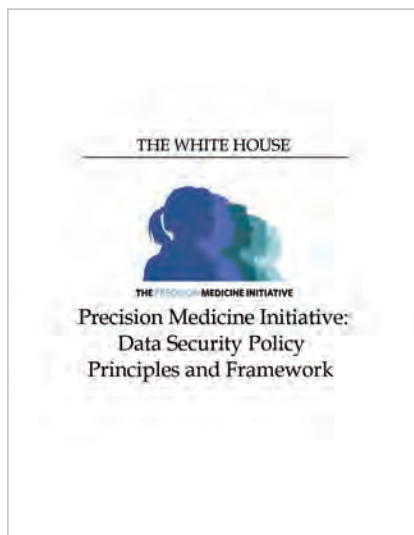


**TABLE 1-2: Joint Program Committees**

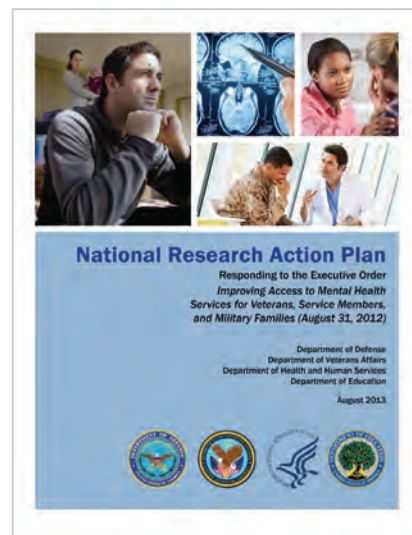
JPC	DHA R&D Directorate Program Areas	Examples of Research Focus Areas
JPC-1	Medical Simulation and Information Sciences	<ul style="list-style-type: none"> <li>• Medical Simulation</li> <li>• Health Information Technology and Informatics</li> </ul>
JPC-2	Military Infectious Diseases	<ul style="list-style-type: none"> <li>• Wound Infections (Prevention, Management, and Treatment)</li> <li>• Pathogen Detection</li> </ul>
JPC-5	Military Operational Medicine	<ul style="list-style-type: none"> <li>• Psychological Health and Resilience</li> <li>• Hearing Loss</li> <li>• Injury Prevention</li> </ul>
JPC-6	Combat Casualty Care	<ul style="list-style-type: none"> <li>• Damage Control Resuscitation</li> <li>• Mild, Moderate, Severe, and Penetrating TBI</li> <li>• Burn Injury</li> <li>• En Route Care</li> </ul>
JPC-7	Radiation Health Effects	<ul style="list-style-type: none"> <li>• Diagnostic Biodosimetry</li> <li>• Countermeasures (Protection and Treatment)</li> </ul>
JPC-8	Clinical and Rehabilitative Medicine	<ul style="list-style-type: none"> <li>• Neuromusculoskeletal Injury</li> <li>• Acute and Chronic Pain Management</li> <li>• Regenerative Medicine</li> <li>• Sensory Systems</li> </ul>

and non-DoD technical experts, make funding recommendations for research and manage research programs under the DHA R&D Directorate in diverse military medical program areas, including those that directly address blast injuries (e.g., JPC-5, JPC-6, JPC-8) (see Table 1-2). These collaborative research programs rely on expertise and capabilities from across the Services, US Department of Veterans Affairs (VA), US Department of Health and Human Services (DHHS), academic centers, industry partners, and other scientific and technical communities.

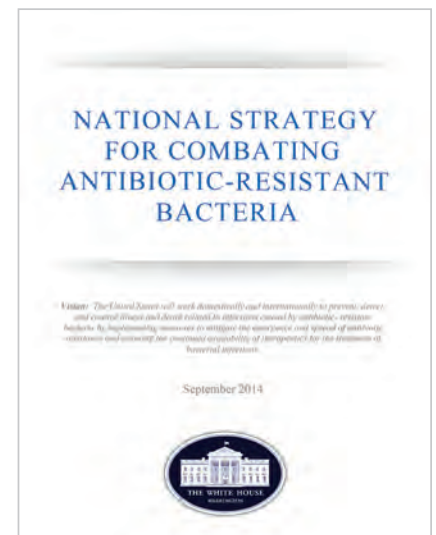
The current emphasis of the DHA R&D Directorate is on the Secretary of Defense (SECDEF)’s stated priorities: Post Traumatic Stress Disorder (PTSD), Traumatic Brain Injury (TBI), prosthetic devices, restoration of eyesight and advancing eye care, and other conditions relevant to battlefield injuries and ailments that affect both Service Members and their Families. These priorities stem from The National Research Action Plan (NRAP) for Improving Access to Mental Health Services for Veterans, Service



Precision Medicine Initiative (White House)



The National Research Action Plan for Improving Access to Mental Health Services for Veterans, Service Members, and Military Families (US DoD, VA, DHHS, and US Department of Education)



National Strategy for Combating Antibiotic-Resistant Bacteria (White House)

Members, and Military Families; the Precision Medicine Initiative; the National Strategy for Combating Antibiotic Resistance; and international scientific partnerships that facilitate global health engagement. The DoD Blast Injury Research Program works with Military Operational Medicine Research Program (MOMRP), Combat Casualty Care Research Program (CCCRP), and Clinical and Rehabilitative Medicine Research Program (CRM RP) to support research that within these priorities.

### **Congressionally Directed Medical Research Programs (CDMRP)**

CDMRP is a global funding organization managing programs in cancer research, military medical research, and other disease- and injury-specific research areas. CDMRP represents a unique partnership between the US Congress, the Military, and the public that uses congressionally directed dollars and core dollars (presidential budget appropriation) to fund groundbreaking, high-impact research awards. The CDMRP works collaboratively with the DHA R&D Directorate JPCs and other members of the DoD medical research community to support DHP and Army research program execution management in several areas relevant to blast injury and military service: injury prevention, traumatic tissue injury, burns, hemorrhage and resuscitation, basic and applied psychological health, PTSD, TBI, neurotrauma, neuroplasticity, wound infections, infectious diseases, prosthetics, vision, hearing, balance, pain, and other rehabilitative and regenerative medicine efforts. Appendix D: Supplemental Tables lists the CDMRP research programs supporting blast injury research.

### **Centers of Excellence (CoE)**

In response to congressional requirements within the NDAA, the DoD established several clinical CoEs. These centers seek to improve clinical care capabilities using new and updated clinical practice guidelines (CPG) and policy recommendations, understand injury and outcome trends, and inform research sponsors about the needs and requirements

of the clinical communities. As a part of their mission, a number of CoEs address blast injury research: the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury (DCoE), National Intrepid Center of Excellence (NICoE), Pain Center of Excellence, Defense and Veterans Center for Integrative Pain Management, Hearing Center of Excellence (HCE), Extremity Trauma and Amputation Center of Excellence (EACE), and Vision Center of Excellence (VCE).

### **Research Forums, Consortia, and Programs Supporting Blast Injury Research**

Numerous ongoing collaborative efforts in the DoD (e.g., working groups, consortiums, research programs) are investigating blast injuries and associated health outcomes. These efforts include the development of new blast injury protective or preventive measures, the development of new treatments for blast injury, and improvements in posttraumatic rehabilitation. For example, the Chronic Effects of Neurotrauma Consortium (CENC) targets mild TBI (mTBI) (including blast-related mTBI) to address knowledge gaps in the basic sciences, determine the effects of mTBI on late-life outcomes and neurodegeneration, identify Service Members most susceptible to these effects, and identify potentially effective treatment strategies. Table 1-3 contains additional examples of collaborative research efforts.

### **Preview of this Report**

The following chapters highlight research efforts to advance the DoD's ability to prevent, mitigate, and treat blast injury. Chapter 2 describes the PCO's activities within the five key EA Mission Thrust Areas: facilitating collaboration, identifying blast injury knowledge gaps, disseminating blast injury research information, shaping research programs to address knowledge gaps, and promoting information sharing and partnerships. Chapter 3 summarizes the PCO's participation in the NATO Human Factors Medicine (HFM)-234 Research Task Group (RTG) and the new NATO HFM-270 (RTG). Chapter 4 focuses on the PCO's role in the MHS Blast Injury Prevention Standards Recommendations (BIPSR)

Process. Chapters 5-7 present the latest updates on blast injury RDT&E supported by the DoD with more detailed discussions of the DCoE and the Warrior Injury Assessment Manikin (WIAMan) science and technology (S&T) project. These chapters also present scientific advancements, improvements in

standards of care, and the development of products to prevent, diagnose, and treat blast injuries. The report concludes with a discussion of the way forward for the Blast Injury Research Program in coordinating and supporting future advancements in blast injury research.

**TABLE 1-3: Examples of DoD Research Forums, Consortia, and Programs Supporting Blast Injury Research**

DoD Entity	Blast Related Efforts
<b>Armed Forces Institute of Regenerative Medicine (AFIRM)</b>	The multi-institutional, multi-disciplinary <b>AFIRM</b> collaborates across numerous agencies to accelerate the development of diagnostic products and therapies for severely wounded Service Members in need of reconstructive treatments. Currently, AFIRM represents 60 projects spread across 33 academic, corporate, and tri-service research institutions.
<b>Auditory Fitness For Duty Working Group (AFFD WG)</b>	One of the priorities of the <b>AFFD WG</b> is to assess occupations and identify hearing-critical tasks within the military. A hearing-critical task is defined as a task in which the detection of sound, understanding of speech, and/or localization of sound are essential for successful accomplishment of action.  The AFFD WG also supports HCE’s mission to heighten readiness and continuously improve the health and quality of life (QOL) of Service Members and Veterans through advocacy and leadership in the development of initiatives focused on the prevention, diagnosis, mitigation, treatment, rehabilitation and research of hearing loss and auditory-vestibular injury.
<b>Bridging Advanced Developments for Exceptional Rehabilitation (BADER) Consortium</b>	The <b>BADER Consortium</b> works with military treatment facilities, VA centers, academia, and industry leaders to target orthopedic care after blast injury. Special areas of interest include improving amputee gait, prosthetics, and QOL issues following extremity injury.
<b>Chronic Effects of Neurotrauma Consortium (CENC)</b>	The <b>CENC</b> is a dedicated joint DoD and VA effort addressing the long term consequences of mTBI in Service Members and Veterans. It is conducted in response to the Presidential Executive Order 13625 and aligned to the National Research Action Plan (NRAP) for Improving Access to Mental Health Services for Veterans, Service Members, and Families. The CENC Coordinating Center is located at Virginia Commonwealth University (VCU) and executes 10 studies and five integrated research cores across 30 participating institutions ( <a href="https://cenc.rti.org">https://cenc.rti.org</a> ). The majority of studies are focused on human subjects recruited from Veteran, Active Duty Service Members, Reserve, and National Guard populations. CENC studies examine chronic TBI and co-morbidities associated with mTBI including: psychological, neurological, sensory deficits (visual, auditory, vestibular), movement disorders, pain (including headache), cognitive, and neuroendocrine deficits.
<b>Pharmaceutical Intervention for Hearing Loss (PIHL) Working Group</b>	The <b>PIHL Working Group</b> develops strategies for standardized analysis of potential systemic and local therapies for hearing loss prevention and rescue.
<b>South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR)</b>	<b>STRONG STAR</b> is a DoD-funded, multidisciplinary, and multi-institutional research consortium that develops and evaluates interventions for the detection, prevention, diagnosis, and treatment of combat-related PTSD and related conditions in active duty Service Members and recently discharged Veterans.
<b>The INjury and TRaumatic STress (INTRuST) Consortium</b>	The <b>INTRuST Consortium</b> was established to combine the research efforts of leading clinical researchers to bring to market novel treatments or interventions for those who suffer from PTSD and/or TBI. The INTRuST portfolio of clinical research and trials spans psychotherapeutics, pharmacotherapeutics, and devices.



DoD Entity	Blast Related Efforts
<p><b>The Consortium to Alleviate PTSD (CAP)</b></p>	<p><b>CAP</b> is a joint VA and DoD effort to understand and treat PTSD and related conditions in active duty Service Members and Veterans. The primary CAP objectives are to focus on the advancement of treatment strategies for PTSD and to identify and confirm clinically relevant biomarkers as diagnostic and prognostic indicators of PTSD and comorbid disorders.</p>
<p><b>Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System</b></p>	<p>The <b>FITBIR Informatics System</b> was initiated as a collaborative effort supported by the DoD CCCRP and the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) as a secure, centralized informatics system developed to accelerate research in support of improved diagnosis and treatment for Service Members and civilians who have sustained a TBI. Under the NRAP, data from DoD and NIH funded clinical TBI studies is required to be inputted into FITBIR. Benefits include 1) accelerating the testing of new hypotheses, 2) allowing multi-study data aggregation to increase the statistical power, 3) providing existing comparator data and 4) identifying patterns not easily extracted from a single study.</p>
<p><b>TBI Endpoints Development (TED) Initiative</b></p>	<p>The <b>TED Initiative</b> was established as a collaborative, multidisciplinary team to advance identification and validation of Clinical Outcome Assessments (COA) and blood-based and neuroimaging biomarkers to be submitted to the US Food and Drug Administration (FDA) Drug Development Tools (DDT) process or the Center for Drug Evaluation and Research (CDER) and/or Medical Device Development Tools (MDDT) of the Center for Devices and Radiological Health (CDRH) pilot qualification process. Decades of TBI research and trials have not yielded any drugs or devices capable of diagnosing or treating mild, moderate or severe TBI. The TED project team leverages DoD, NIH, and foundation-funded research networks and infrastructure, as well as several TBI study datasets containing thousands of TBI subjects to harmonize and curate data into a large Metadataset. The project will validate dataset of mild-moderate-severe TBI endpoints and enter into FDA qualification processes to become acceptable standard measures for clinical trials of TBI diagnostics or therapeutics and provide a clear path to market. Specifically, the overarching objective is to leverage existing research and clinical infrastructure (TRACK-TBI, CENC, and the Concussion Research Consortium) to qualify COAs and biomarkers for FDA DTT/MDDT process. Working with the Clinical Data Interchange Standards Consortium (CDISC), the TED research consortium will identify and validate clinically relevant endpoints for diagnostic and therapeutic trials to conform TBI Common Data Elements (TBI-CDE version 2) to CDISC data standards for trials involving diagnosis and treatment of mild, moderate, and severe TBI subject to FDA regulatory submission.</p>
<p><b>The National Collegiate Athletic Association (NCAA)-DoD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium</b></p>	<p>The <b>CARE Consortium</b> is a joint DoD and NCAA research effort dedicated to studying concussion to better understand the development of injury and trajectory of recovery. The CARE Consortium has enrolled over 30,000 student athletes and service academy cadets at 30 sites. The Consortium has two study arms, the first being a clinical study focused on examining the natural history of concussion with a multi-site, longitudinal investigation of concussive and repetitive head impacts. The second arm builds upon the first arm, with a clinical study allowing for more advanced research projects, such as testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging. The CARE Consortium, and the data the team has and will continue to collect, will allow scientists to develop evidence-based approaches to understanding the risks, management, and possible treatment strategies for concussion.</p>
<p><b>Center for Neuroscience and Regenerative Medicine (CNRM)</b></p>	<p><b>CNRM</b> was established by Congressional action (Public Law 110-252) as an intramural federal traumatic brain injury research program focused on the study of blast injury to the brain and posttraumatic stress in warfighters. Today, the CNRM involves over a hundred federal intramural investigators in the National Capital Area from within the DoD and the NIH. The CNRM truly acts as a research “center” which integrates the expertise of clinicians and scientists across numerous disciplines to catalyze innovative approaches to TBI research. The CNRM research programs have an emphasis on aspects of high relevance to the military populations, particularly Service members cared for at the Walter Reed National Military Medical Center (WRNMMC) and those exposed to blast events. USUHS is responsible for the overall operational and fiscal management of the CNRM, on behalf of the DoD.</p>



02



CHAPTER 2:

# DOD BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

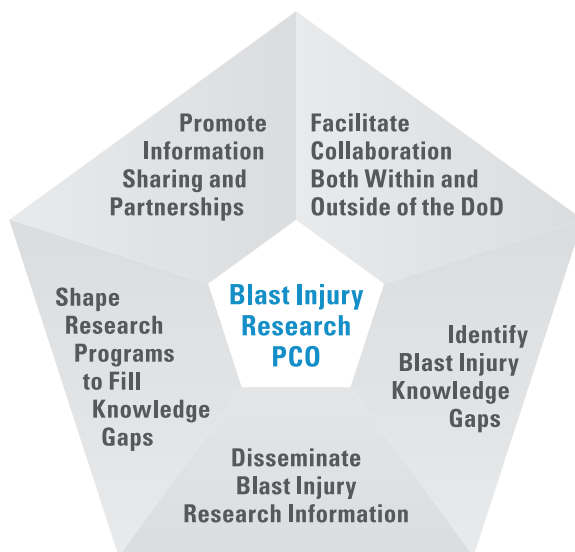


The DoD Blast Injury Research PCO supports the DoD EA by coordinating blast injury research investment within and outside of the DoD, both nationally and internationally, to support the delivery of timely and effective blast injury prevention, mitigation, and treatment solutions for Service Members. The PCO's activities help to identify and address knowledge gaps, disseminate information, and minimize duplication of effort within the DoD. The PCO promotes collaboration among researchers across the DoD, other federal agencies, academia, industry, and international partners to solve complex challenges related to blast injury. It takes full advantage of the body of knowledge and expertise that resides both within and beyond the DoD.

### Key FY16 PCO Activities in Support of EA Mission Thrust Areas

In response to DoDD 6025.21E, Commander, MEDCOM established the PCO to assist in fulfilling EA responsibilities and functions and coordinating DoD blast injury research efforts and programs. The PCO executes its mission by supporting five key EA Mission Thrust Areas (see Figure 2-1). Below are examples of FY16 PCO activities supporting each of the five EA Mission Thrust Areas.

**FIGURE 2-1: PCO Support of EA Mission Thrust Areas**



#### MISSION

Support the DoD EA by:

- Coordinating DoD-sponsored biomedical research programs aimed at preventing, mitigating, and treating blast-related injuries
- Identifying knowledge gaps and shaping research programs accordingly
- Promoting information sharing among the operational, intelligence, medical, and materiel development communities
- Facilitating collaborative research among DoD laboratories and the laboratories of other federal agencies, academia, and industry to leverage resources and take full advantage of the body of knowledge that resides both within and outside of the DoD to accelerate the fielding of blast injury prevention and treatment strategies.

#### VISION

A fully coordinated DoD Blast Injury Research Program, as envisioned by Congress and directed by the Secretary of Defense, that delivers timely and effective blast injury prevention, mitigation, and treatment strategies to our Service Members today and in the future.

### Facilitate Collaboration Within and Outside of the DoD

In support of the EA responsibility to promote collaboration on blast injury research topics, the PCO actively engages stakeholders within the DoD and across federal agencies, academia, and industry—both nationally and internationally. The following examples demonstrate the PCO's collaborative efforts with domestic and international partners.

#### International Collaboration through NATO HFM-234 (RTG)

The PCO continues to chair NATO HFM-234 (RTG), "Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods and Standards," whose membership includes blast injury research experts from nine NATO nations. Since its inception in 2013, the HFM-234 (RTG) has focused on standardizing animal models of blast injury; creating common methods for establishing dose-response and



route of exposure; generating computational models; specifying dose regimens relevant to human medical endpoints; and developing methods for translating basic research to medical products and/or improved protection for Service Members. Approaching the end of its term in July 2016, the PCO chaired the sixth and final working meeting in January 2016 at Porton Down in the United Kingdom to review, amend, and agree on the five deliverables: 1) Guidelines for Conducting Epidemiological Studies of Blast Injury; 2) Guidelines for Reproducing Blast Exposures in the Laboratory; 3) Guidelines for Using Animal Models in Blast Injury Research; 4) a comprehensive Dictionary of Blast Injury Terms; and 5) a final Technical Report on HFM-234 activities. These deliverables will be published as official NATO documents and disseminated throughout the blast injury research community, both nationally and internationally, to promote international collaboration and cross-study comparison through standardized research methodologies. See Chapter 3 for more information on the PCO's collaboration with NATO.

### **US-India Collaboration on Experimental and Computational Studies of Blast and Blunt TBI**

The PCO continues to be a key player in the Defense Trade and Technology Initiative (DTTI), an international partnership organized by the USD(AT&L) and the Indian Ministry of Defence, Defence Research and Development Organization (DRDO). Under the US-India DTTI, the PCO and MOMRP initiated a project titled, "Experimental and Computational Studies of Blast and Blunt Traumatic Brain Injury." The lead collaborative organizations are the USAMRMC and the Institute of Nuclear Medicine and Allied Sciences (INMAS)-DRDO, Ministry of Defence, India. Other participants include the Biotechnology High Performance Computing Software Applications Institute (BHSAI), New Jersey

Institute of Technology (NJIT), Walter Reed Army Institute of Research (WRAIR), Naval Research Laboratory (NRL), Indian Defense Institute of Psychological Research (DIPR), and Indian Terminal Ballistics Research Laboratory (ITBRL). Project objectives include:

- Develop and validate a blast injury animal model for mTBI using imaging, histological, cognitive, and behavioral analyses
- Develop, validate, and cross-validate a computational model for blast and blunt injury
- Develop anatomically accurate head/brain models for blast/blunt injuries from clinical and experimental data
- Develop injury severity scale for blast-induced mTBI

The objective of this project is to create blast injury animal models of mTBI to help elucidate the mechanism of injury. Validated computational/anatomical models can expedite identification, selection, and transition of prevention and treatment strategies to clinical trials. Validated animal models could also be translated to commercial defense industry for designing improved PPE. The injury severity scale for blast-induced mTBI could be used to inform MHS clinical practices in theatre and during treatment.

### **Identify Blast Injury Knowledge Gaps**

Understanding the current state of the science on blast injury is critical to identifying knowledge gaps, the appropriateness of research efforts, and the direction of future efforts. In FY16, the PCO continued to streamline the BIPSR Process, aiming to be more effective and efficient at identifying gaps in available candidate MHS Blast Injury Prevention Standards; this process directly supports the key EA responsibility of recommending standards for ASD(HA) approval and DoD use.

### **Applying the BIPSR Process to Assess Candidate MHS Blast Injury Prevention Standards:**

The PCO continues to implement the BIPSR Process with support from the MITRE Corporation, a DoD trusted agent that operates Federally Funded Research and Development Centers (FFRDCs). The BIPSR Process is designed to identify and objectively evaluate the details of available blast injury prevention standards to determine their suitability for use by the DoD in health hazard and survivability assessments, as well as protection system development. In FY16, the BIPSR Process Evaluations for the Spine and Back and Upper Extremity Blast Injury Types were completed, and critical needs for developing future MHS Blast Injury Prevention Standards in these areas were identified. In addition, the PCO introduced the Interactive Blast Injury Prevention Standards Recommendation (iBIPSR) capability, a web-based collaboration environment that is expected to enhance information sharing among blast injury experts and support the PCO's EA mission to leverage existing knowledge and foster collaboration by providing a platform for continuous collaboration throughout the BIPSR Process. In collaboration with MITRE, the PCO began to prove out the iBIPSR capability using the Auditory Blast Injury Type as exemplar. To ensure that the current needs of the operational environment and DoD are being met, the PCO initiated a reprioritization effort for the remaining MHS BIPSR Process Blast Injury Types. For more information on the FY16 BIPSR Process activities, please see Chapter 4.

### **Disseminate Blast Injury Research Information**

Proper dissemination of blast injury research information ensures that all stakeholders along the RDT&E continuum, from laboratory to field, are equipped with the most timely, up-to-date information. Dissemination of this information occurs through multiple channels, including formal reporting mechanisms, direct requests for information (RFI) to the PCO, and stakeholder community briefings.

#### **Annual Report to the EA**

The PCO prepares an annual report to the EA covering S&T efforts and programs focused on the prevention, mitigation, and treatment of blast injuries. Intended to inform senior DoD policymakers, fellow researchers, and public audiences, this report covers fiscal year blast injury research accomplishments across the DoD that address the full spectrum of blast injuries. The FY16 annual report is available on the PCO website (<https://blastinjuryresearch.amedd.army.mil>).

#### **Preservation and Dissemination of DoD Historical Blast Data**

The PCO launched a significant project to preserve and disseminate DoD historical blast bioeffects research data collected at the Albuquerque Blast Test Site on Kirtland Air Force Base (AFB), New Mexico, over a period of nearly five decades, from 1951 to 1998. The goal of this effort is to provide broad access to the considerable wealth of DoD historical data and findings on the biological effects of blast so that program managers (PMs), researchers, and medical decision makers can solve current and future problems with a minimum of duplication and a maximum of efficiency. The four major steps of the project include: (1) recovery of historical data into a form that is complete, organized, and can be readily accessed; (2) qualification of the data to ensure that the data is reliable and consistent; (3) development of a



Photo credit: PFC Daniel Parrott/US Army

web-based application that allows controlled access to the data, literature, and findings; and (4) population of an online data repository with user tools for ongoing data collection and user interaction. The historical data will be recovered and disseminated in four phases based on the blast effects mechanisms studied: primary, tertiary, secondary, and combined threat. As the historical and contemporary blast bioeffects data are captured and made available, the scientific community will be able to begin testing hypothesis and validating proposed models. The potential payoff includes the preservation and wide availability of the data to researchers and the scientific community; guidance to research PMs on past research/data to avoid unnecessary duplication, speed up addressing gaps, and validate new models and hypotheses; guidance to protection system developers to support the development of effective protection systems; and guidance to medical decision makers on screening algorithms and countermeasures for blast injuries. This project supports the EA's responsibility to disseminate information so that research programs can leverage historical knowledge and plan future research

investment to addresses remaining knowledge gaps and avoid unnecessary and duplicative work.

### Shape Research Programs to Fill Knowledge Gaps

The PCO helps to shape blast injury research programs by actively participating on research program planning, management, and advisory committees. Being an active participant ensures that key blast injury knowledge gaps are addressed, encourages collaborative research efforts, and identifies potentially duplicative research.

### Shaping Research through JPCs

The PCO's continued participation on JPCs ensures that high priority blast injury research issues are addressed in future medical research investments. In FY16, the PCO participated in a business meeting for the Military Infectious Diseases Research Program (MIDRP, JPC-2); three In-Progress Review (IPR) meetings for the CRMRP, (JPC-8); an integrating integrated product team (IIPT) meeting and business meeting for the MOMRP, (JPC-5); and an IIPT meeting for the CCCRP, (JPC-6). These



meetings provide a high-level snapshot of the key areas of each program’s medical research investment and highlighted the importance of DoD/VA coordination and collaboration with researchers from other federal agencies, academia, and industry. They also underscore the remaining knowledge gaps, requirements, and challenges facing each research area.

## Promote Information Sharing and Partnership

Given the complex nature of blast injury, information sharing and partnerships are critical to advancing blast injury RDT&E through coordinated efforts across stakeholder communities. In FY16, the PCO participated in several activities to promote information sharing and strengthen partnerships with key national and international organizations.

### **Sharing Research Findings on Blast-related Auditory Injury and Neurodegeneration**

The PCO joined researchers and other PMs to discuss two key blast injury research areas—auditory injury and TBI following blast exposure—in a meeting titled, “DoD Research Meeting on Auditory Health and Neurodegeneration.” Sponsored by the USAMRMC and the DoD HCE, the multidisciplinary group discussed new research findings that demonstrate how auditory neural pathways mediate pathogenic changes following blast exposure, and explain symptoms typically associated with mTBI and psychological health issues. Current research also shows how traditional metrics for hearing loss, threshold shifts, and cochlear hair cell counts, may be missing a more important injury endpoint involving the loss of inner hair cell synapses of auditory nerve fibers that disrupt neural signals to the brain and may occur before declines in threshold sensitivity or hair cell counts. These research findings suggest a new approach is needed to address auditory health and neurodegeneration. This new approach requires coordination across research disciplines and research programs.

### **Strengthening Partnerships to Optimize Health through Technology**

The PCO continues to represent the EA by participating in meetings and workshops to share information and strengthen partnerships to address key blast injury research priorities. The PCO participated in a workshop titled, “Developing Joint ‘Wearable’ Technologies to Optimize Warfighter Health and Performance,” sponsored by the Office of the ASD(HA), Office of the ASD(R&E), and DHA. The objective of the workshop was to explore the scope of DoD S&T efforts to develop wearable technologies for monitoring Service Member health and performance. Currently, there is no DoD-wide research agenda or coordinated roadmap for wearable technologies that would be capable of monitoring and tracking Service Member physiological data across a wide range of parameters. During the workshop, S&T overviews on wearable technologies were provided by each of the Services as well as presentations by the USSOCOM, DARPA, Defense Threat Reduction Agency (DTRA), US Army Research Laboratory (ARL), and USAMRMC. In addition, a presentation on the state-of-the-art of commercial wearables was presented by the Massachusetts Institute of Technology (MIT) Lincoln Laboratory. Sponsors of this workshop will deliver a report that articulates the DoD wearable technology landscape, identifies key objectives and challenges, and highlights areas for coordination and collaboration, improving communication and partnerships across the DoD research community working in this domain.

### **International State-of-the-Science (SoS) Meeting Series**

The International SoS Meeting series has been a forum for knowledge sharing, collaboration, and communication across blast injury research communities since 2009. Each PCO-hosted meeting brings together the world’s top researchers and experts from across the DoD, other federal agencies, academia, industry, and international partners to share expertise and cutting-edge research on a specific topic related

to blast injury. Resulting recommendations shape future blast injury research priorities and facilitate the development of blast injury prevention, mitigation, and treatment strategies for the Service Member.

## 2015 International SoS Meeting

Blast-related injury is a potential threat to the health and performance of Service Members. Repeated exposure to blast-related TBI may induce long-term neurodegeneration and chronic medical needs. Questions about the potential association between head injury and Chronic Traumatic Encephalopathy (CTE) have been raised amidst brain health concerns for military and contact sports populations. To address these questions, the PCO organized the 2015 International SoS Meeting on the potential relationship between blast-related trauma and CTE, titled “Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?”

The objectives of the meeting were as follows:

- Discuss the evidence linking repeated blast exposure to neurodegeneration
- Assess the pathophysiology, underlying mechanisms of injury, and progression of blast-induced neurodegeneration
- Identify specific features that can contribute to the characterization of CTE as a unique neurodegenerative condition
- Examine relevant animal injury models for blast-induced neurodegeneration
- Discuss strategies for prevention, mitigation, early diagnosis, and treatment of blast-induced neurodegeneration
- Explore the link between blast-induced neurodegeneration and CTE
- Identify the knowledge gaps that will inform future research directions

## Literature Review

To inform the 2015 International SoS Meeting, the PCO requested a review of recent research literature on CTE. This literature review addresses specific research questions about (1) the pathophysiological basis of CTE and (2) associations between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE.

CTE is described as a neurodegenerative disorder affecting individuals exposed to head injury that can result in a range of cognitive, behavioral, and/or motor deficits. Broad scientific consensus about CTE has not been established; however, multiple academic and government organizations are investigating links between exposure to brain injuries, CTE-associated pathology, and reported clinical symptoms.

The current state of the science has generated an initial consensus on the neuropathology of CTE<sup>4</sup>. However, the evidence does not allow for a conclusive determination of whether exposure to head injury is sufficient and causative in the development of CTE pathology. All existing clinical neuropathological evidence associated with CTE has been gathered from postmortem autopsy of subjects with histories of exposure to head injury. Unique pathological characteristics of CTE have not been comprehensively determined, in part because observations of macroscopic (e.g., gross anatomical) and microscopic (e.g., molecular) abnormalities vary to some degree across different studies and research groups. Based on existing observations, research groups have proposed classification frameworks describing CTE as a progressive disease or as a collection of related neuropathologies.

Existing research does not substantively inform whether the development of CTE is potentially associated with head injury

frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact, nonimpact, blast). Head injury exposure data is not consistent across case studies, which prevents systematic analysis. Many CTE studies characterize head injury exposure as exposure to sport or occupation and do not include data describing injury frequency, severity, or the time elapsed between injuries. The incidence of CTE-associated pathology and/or symptoms in at-risk populations cannot be determined from existing literature and highlights a need for population-based studies. While the primary risk factor for CTE is thought to be exposure to head injury, additional research is needed to investigate other potential risk factors, such as genetic predisposition. The broad range of clinical symptoms associated with CTE overlap with those of multiple neurodegenerative disorders.

Animal models may also offer insights to neuropathological and neurobehavioral abnormalities thought to be associated with CTE. While animal models do not accurately exhibit the neuropathology of CTE, animal models of traumatic brain injury (TBI) may reflect some associated head injury exposure conditions (e.g., blunt force or blast-induced) and tau pathology.

Successful development of biomarkers to identify CTE pathology in living persons would benefit the research and development of potential diagnosis, prevention, and treatment strategies. Investigators are pursuing neuroimaging modalities and biospecimen analytes as potential predictive biomarkers of CTE by targeting pathophysiological phenomena associated with CTE and the biological processes affected by head injury exposure. Because no established treatment for CTE exists, current mitigation strategies focus on preventing head injury and/or concussion. Although consensus on the understanding of CTE is still being established, researchers

are investigating potential treatment approaches that target the pathophysiological mechanisms associated with CTE. Because of the neuropathological similarities with Alzheimer's disease and TBI, potential pharmacological and behavioral interventions for these conditions are also being investigated for CTE.

The current state of the science does not allow for a conclusive determination of whether exposure to head injury is associated with the development of CTE pathology or clinical symptoms. Existing clinical data are limited, observational in nature, and subject to several methodological concerns, leading some researchers to question whether CTE is a unique neurodegenerative disease. CTE has drawn significant public and media attention given the large at-risk population (e.g., military Service Members, contact sport athletes). Experts have noted concern over the potential clinical and legal consequences of widespread misunderstanding of CTE. In light of these factors, the need for additional research is clear, particularly population-based studies, the use of standardized pathology protocols, and the development of clinical diagnostic criteria.

### **November 2015 Meeting**

The 2015 International SoS Meeting on, "Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?" took place from 3 to 5 November, 2015, in McLean, Virginia. The meeting's Planning Committee included clinical, research, and program representatives from the DoD, NIH, National Football League (NFL), NCAA, and One Mind. The role of the Planning Committee was to refine meeting objectives, oversee and provide feedback for the literature review, formulate working group questions, and solicit and rank meeting presentations. The Planning Committee also identified six members to serve as the Expert Panel, each charged with



chairing the working group sessions and identifying the major meeting findings and recommendations needed to advance the state of the science with respect to the potential relationship between blast-related trauma and CTE.

One hundred twenty-four participants from the DoD, VA, NIH, academia, medical community, industry, and international organizations attended the meeting. The agenda consisted of presentations, a poster session, concurrent working group sessions, and Expert Panel member briefings summarizing the findings from working group sessions. Following the meeting, an Expert Panel session reviewed meeting data and formulated recommendations. Selected presentations from the SoS Meeting are available from the PCO website at: <https://blastinjuryresearch.amedd.army.mil/sos>.

### **Expert Panel Findings**

The Expert Panel noted that the majority of blast-related TBIs within the military population arise from a mixed exposure to both blast overpressure (BOP) and impact as opposed to BOP alone; this complicates the meaning of “blast” when discussing blast-related trauma. The pathology of TBIs and any subsequent neurodegenerative outcomes arising from either of these exposure types is largely unknown. As a result, the overarching finding identified by the Expert Panel is that existing scientific evidence is insufficient to link blast-related TBI with CTE. The Expert Panel identified thirteen findings describing research and knowledge gaps, clinical gaps, and research opportunities that, if addressed with focused effort, would further the understanding of the potential relationship between blast-related neurotrauma and CTE.

### **Research and Knowledge Gaps**

There is a lack of blast exposed clinical tissue, with well-annotated medical and blast exposure histories, available for

neuropathological analysis. Limited opportunity to gather neuropathological evidence with historical data impede the ability to explore the association between neuropathology and lifetime risk factors or clinical features. Better understanding of the human neuropathology of blast and any associated neurodegeneration is needed to develop informative animal models.

Standard definitions of “blast” and “blast exposure” are needed. Blast-related exposures can encompass all types of blast injury, from primary to quinary. However, different preclinical and clinical investigations model or define blast differently, which introduces variability across studies and limits reproduction and validation of findings.

Existing animal models are inadequate to study blast-related TBI and neurodegeneration. Validated and clinically-relevant animal models are needed to identify underlying mechanisms of acute and chronic blast injury. Absent an understanding of injury mechanisms, the discovery of diagnostics and treatments is greatly inhibited.

Longitudinal and prospective studies, both having a strong neuropathological component, are needed to characterize the risk factors and spatiotemporal development of CTE. Informed by the current state of the science, well designed studies that collect detailed medical histories and exposures (frequency, magnitude) from Service Members and Veterans, and obtain consent for brain donation by these individuals, can help establish the role of blast-related neurotrauma in the development of CTE.

Limitations to data access and data sharing impose significant barriers to research. Legal, ethical, and logistical barriers to the use of Service Member and civilian health data, exposure history, and medical records prevent analysis of potentially useful clinical information. Promoting broader access and

use of these extant data could result in rapid answers to outstanding questions on the potential relationship between blast exposure and CTE.

Substantiated risk factors for CTE are unknown, with the exception of exposure to head trauma. Studies of other potential risk factors, including gender, age, psychological health, drug or alcohol abuse, and genetics, have not been conclusive.

Evidence-based RTD protocols are lacking. There is no existing scientific evidence establishing parameters of existing DoD RTD guidelines, which are based on clinical symptoms, as protective against the risk of neurodegeneration.

### **Clinical Gaps**

Clear and standardized clinical criteria for CTE are lacking, impeding progress in development of premortem diagnosis and screening approaches. Because the clinical features associated with CTE overlap with other neurodegenerative conditions such as Alzheimer's disease, identification of specific or unique clinical diagnostic criteria has been difficult. Standardized neuropsychological and behavioral assessments relevant to CTE are also lacking. Definition and diagnosis of CTE should ultimately be driven by clinicopathological approaches that incorporate clinical and pathological information. Defining and describing CTE as a spectrum disease, rather than as a binary condition, should also be considered.

Development of fluid and imaging biomarkers are needed for diagnosis and treatment of CTE. Non-invasive biomarkers of CTE would enable premortem diagnosis and serve to assess the efficacy of therapeutic strategies.

Current neuroimaging approaches cannot diagnose CTE, or distinguish CTE from other neurodegenerative disorders. Neuropathological abnormalities associated with CTE, such as tau or Amyloid beta protein aggregation, cannot be characterized reliably with existing neuroimaging technology. Spatial resolution



Photo credit: US Air Force

of existing neuroimaging modalities is also insufficient to image neuropathology at the scale observed in CTE studies.

### **Research Opportunities**

Existing data can be used to investigate CTE risk factors. Clinical correlation studies of electronic health record data and/or concussion care clinics should be explored. Populations exposed to blast should be continuously monitored. Monitoring may help to determine a dose-response relationship between blast intensity and frequency, and severity of human injury. Once a dose-response curve is established in humans, it will become easier to create more accurate animal models of blast injury.

Sensor technology development and materials science offer significant research and prevention opportunities. PPE-embedded blast wave sensors could allow objective measurement to supplement, or replace, exposure documentation. Sensor-enabled detection of rotational acceleration, which may play a role in blast-related mid-brain and cerebellar injury, may be valuable. Advanced materials research can benefit sensor technology development, as well as personal and vehicular protection.

### Expert Panel Recommendations

The Expert Panel identified six recommendations describing specific actions needed to advance research exploring the potential relationship between blast-related neurotrauma and CTE. Table 2-1 describes Expert Panel recommendations, including immediate (< 1 year), short term (1-2 years), midterm (3-4 years), and long term (5+ years) timeframes for addressing necessary components of these recommendations.

Among the six recommendations, the

Expert Panel identified the first four as highest priority for addressing pressing research needs. These four high-priority recommendations include, in order of priority: 1) more collection and study of clinical neuropathology samples, 2) standardization of clinical diagnostic criteria, 3) development of clinically-appropriate and standardized animal models, and 4) development of non-invasive serial assessment strategies (e.g., imaging or biospecimen biomarkers).

**TABLE 2-1: Expert Panel Recommendations**

Recommendation	Timeframe	Components
Create a coordinated brain bank/repository system, accessible to the research community	Immediate (< 1 year)	Educate researchers on the importance of neuropathology and provide communication strategies that would enable them to advocate for brain donation with participants and families  Address logistical barriers of brain donation to promote rapid acquisition of brain tissue and facilitate sharing within research community
	Short Term (1–2 years)	Establish a central repository and laboratory for storing, processing, and analyzing brains  • Collect 100 brains
	Mid Term (3–4 years)	Develop definitive criteria for establishing the pathology of blast exposure
	Long Term (5+ years)	Collect 1,000 brains, including medical and blast exposure history  • For brains acquired <48 hours postmortem, fix one hemisphere (e.g., for immunostaining) and freeze the other hemisphere (e.g., for <i>in situ</i> hybridization)  • For brains acquired >48 hours postmortem, fix both hemispheres
Develop standardized clinical diagnostic criteria	Short Term (1–2 years)	Gather exposure data from pre-enlistment and pre- and post-deployment time periods  Use standardized neuropsychological/behavioral assessments validated for serial use in subjects with suspected blast-related neurodegeneration  Continue development of biospecimen biomarkers of injury to complement exposure histories
	Long Term (5+ years)	Follow subjects with blast exposure, with potential exposure, and age-matched controls long term to determine the incidence of blast-induced neurodegeneration



Recommendation	Timeframe	Components
Develop and validate animal models clinically relevant to blast injury and chronic neurodegeneration	Short Term (1–2 years)	Develop standardized protocols with blast exposure characteristics Measure outcomes at longer time points following blast exposure that more appropriately reflect chronic effects Share protocols across the research community
Develop a strategy for development of next-generation biospecimen and imaging biomarkers	Immediate (< 1 year)	Convene an expert panel to assess current biomarkers and make recommendations for future development of technologies, protocols, and analytics
	Short Term (1–2 years)	Develop a long-term plan for standardizing biomarker measurement
	Mid Term (3–4 years)	Explore combinatorial imaging modalities for differential diagnosis
	Long Term (5+ years)	Develop high spatial resolution neuroimaging approaches to detect potential neuroanatomical characteristics specific to CTE
Strengthen ongoing longitudinal and prospective studies, or initiate new studies to explore the spatiotemporal development of CTE and candidate risk factors, respectively; emphasize neuropathological analysis of blast-exposed tissue	Immediate (< 1 year)	Convene an objective expert panel to: <ul style="list-style-type: none"> <li>• Identify gaps in current longitudinal studies that can be addressed with additional data (e.g., neuropathological tissue)</li> <li>• Review current prospective studies to determine if risk factors are adequately addressed</li> </ul> Plan a prospective study using candidate risk factors, potential biomarkers, and tissues that would address remaining gaps Identify additional potential risk factors for analysis which may include genetic susceptibility, gender, age, drug abuse, and performance-enhancing drugs
	Short Term (1–2 years)	Initiate recruitment and data collection with an emphasis on neuropathological analysis of blast-exposed tissue
	Long Term (5+ years)	Analyze prospective data to determine which candidate risk factors and biomarkers can be quantified
Implement prevention and mitigation strategies until treatment strategies become available	Immediate (< 1 year)	Modify training protocols to reduce exposure (without reducing training time) Educate military instructors about long term exposure risks Maintain optimal brain health in Service Members (e.g., sleep, etc.) Reinforce existing guidelines for management of mTBI
	Long Term (5+ years)	Improve equipment (PPE and vehicles) to mitigate injury Determine extent to which RTD guidelines mitigate risk of neurodegeneration

## 2016 International SoS Meeting on Minimizing the Impact of Wound Infections Following Blast-Related Injuries

In FY16, the PCO planned the 2016 International SoS Meeting, which is focused on “Minimizing the Impact of Wound Infections Following Blast-Related Injuries.” The objectives of the meeting are as follows:

- Determine predictive risk factors for wound infections following blast-related injuries, including individual susceptibility and environmental contributions, from point of injury through continued hospital care
- Identify candidate biomarkers that would enable rapid and accurate diagnosis, management, and prognosis of wound infections following blast-related injuries
- Examine prevention strategies, including vaccines, for mitigation of wound infections following blast-related injuries
- Propose strategies that would mitigate the impact of multi-drug resistant, virulent, or opportunistic organisms on wound infections following blast-related injuries

### Literature Review

To inform the 2016 International SoS Meeting, the PCO requested a review of recent research literature directed at minimizing the impact of wound infections following blast-related injuries. This literature review addresses specific research questions about: 1) predictive risk factors of wound infection following blast-related injuries; 2) identification of candidate biomarkers to advance wound infection diagnosis capabilities; and 3) emerging prevention and treatment strategies, including vaccines, in an era of antimicrobial resistance.

Wound infection following blast-related injuries continues to be a significant source of morbidity and mortality in the modern era of military healthcare. Approximately a quarter of combat wounds become infected, having significant impact on patient outcomes and healthcare costs. Several studies report increasing rates of nosocomial infections as patients experience prolonged hospitalization and progress through higher echelons of care.

Additionally, combat wound infections due to drug-resistant or multidrug-resistant organisms have increased in military personnel that served in Iraq and Afghanistan.

Risk factors associated with combat wound infection include injury characteristics, such as mechanism of injury, severity of injury, and region of injury. Environmental characteristics and healthcare-associated exposures, such as blood transfusions, medical implants, and delayed antibiotic treatment, also contribute to increasing risk of infection. Improved approaches to diagnose and detect infection would promote better prediction of infection, earlier diagnosis, earlier treatment application, individually-tailored treatments, and improved understanding of the epidemiology of wound infection.

While CPGs are in place to guide detection and diagnosis of wound infection, and provide recommendations for post-injury antimicrobials and antifungals, debridement and irrigation, surgical wound management, and facility infection control measures for implementation from prehospital field care to regional Level IV hospitals; limited information is available about specific diagnostic capabilities across military treatment facilities. Development of novel objective biomarkers would enable faster and more precise wound infection diagnosis capabilities. National and international researchers from government, private, and non-profit organizations are seeking to develop novel infection biomarker approaches, including proteins and enzymes, proteomic analysis, metabolomics, next-generation sequencing, biofilm detection, electrochemical sensors, intelligent wound dressings, and digital microscopy.

In addition, these organizations are collaborating to develop new prevention and treatment approaches as alternatives to antimicrobials, including vaccines, passive immunological therapy, phage therapy, antimicrobial peptides, photodynamic therapy, quorum sensing, nanoparticles, iron chelators, lectin inhibitors, FimH inhibitors, lactoferrin,

hypothiocyanite, bioengineered tissue, bacterial gene transfer, probiotics, and plant compounds.

Challenges posed by the provision of healthcare in austere environments, increasing nosocomial transmission, and the emergence of drug-resistant infection present capability gaps in the mission to minimize wound infection following blast-related injury. To bridge these gaps, experts have identified various research needs in three areas. First, basic science studies designed to achieve a better understanding of physiological processes including the pathophysiology of infection and the host immune response to infection, the association between biofilms and infection, and the mechanism of action for existing antibiotics and immunoprotection. Secondly, studies focused on the military healthcare system including continued epidemiological assessment of bacterial and fungal infection, assessment of the availability and use of diagnostic techniques for wound infection, and assessment of the delivery of antimicrobials following injury and subsequent infection rates. Third, studies advancing the development of novel products or methods enabling new diagnosis, prevention, and treatment approaches including biomarkers including biofilm detection methods, new vaccine candidates, and improved animal models that more accurately reflect clinical wound infection

### **Planning the Meeting**

The meeting's Planning Committee included 26 representatives from the Services, DoD medical and nonmedical communities, other federal agencies, academia, and the US Army's FFRDC, RAND Army Research Division. The Planning Committee identified six Subject Matter Experts (SMEs) to serve as the Expert Panel, whose role it is to lead discussions, ask tough questions, and challenge assumptions to tease out what is known and unknown in the field, as well as ways for moving the field forward.

The 2016 International SoS Meeting on Minimizing the Impact of Wound Infections Following Blast-Related Injuries will be held in early FY17 and up to 120 participants are expected to attend the meeting, including

representatives from the DoD, NIH, VA, industry, and academia. The meeting will include plenary sessions with key topic and scientific presentations, poster sessions, and six working groups led by Expert Panel members.

The working groups will develop answers to the following questions:

- How can our understanding of risk factors of wound infections, bacterial or fungal, following blast-related injuries, be applied to advance prediction, prevention, detection, and treatment strategies?
- What candidate biomarkers, from either host or pathogen, can potentially enable rapid and accurate diagnosis, management, and prognosis of wound infections and biofilm formation following blast-related injuries?
- What prevention strategies, to include the use of vaccines, can be employed to reduce the incidence of wound infections across the continuum of care (point of injury to US military hospital setting) following blast-related injuries?
- What strategies hold the most promise for the treatment of wound infections associated with blast-related injuries and what are the challenges in fielding these?

After the meeting, the Expert Panel members will meet to synthesize the findings and develop recommendations related to minimizing wound infections following blast-related injuries. The PCO will prepare a detailed report summarizing the meeting proceedings, findings, and recommendations that will be distributed to key stakeholders and made publicly available on the PCO website. A more detailed description of the meeting and its outcomes will be described in the FY17 EA Report.

### **DoD Brain Health Research Program Coordinator**

In FY16, the PCO created and filled a new position for a Brain Health Research Program Coordinator. This role supports EA responsibilities to disseminate brain health research and clinical practices information, facilitate collaboration, and promote information sharing among researchers and clinicians not only within the



DoD but in other federal agencies, academia, and industry, both within the US and internationally. Coordination activities focus on brain health research topics identified in Public Law 109-163, specifically:

- Medical technologies and protocols to more accurately detect and diagnose blast injuries, including improved discrimination between TBI and mental health disorders
- Integrated treatment approaches for Service Members who have a combination of TBI and mental health disorders or other injuries
- Improved clinical evaluation and treatment approaches for blast injuries with emphasis on TBI and other consequences of blast injury
- The incidence of TBI attributable to blast injury in Service Members returning from combat
- TBI treatment programs that enhance the evaluation and care of Service Members with TBI in medical facilities in the US and in deployed medical facilities, including those outside of the DoD.
- Organize and oversee multidisciplinary expert panels and SoS meetings to identify brain health knowledge gaps and recommend medical research and clinical practices that will close these gaps
- Participate in the medical S&T planning and review activities of the DoD and Services to identify opportunities for collaboration, to advise on brain health knowledge gaps, and to ensure that current and future research adequately addresses the recognized gaps
- Serve as the EA's representative for the implementation of the NRAP which was directed by Executive Order to improve coordination among the DoD, VA, Health and Human Services, and Education on research efforts relating to TBI, PTSD, and other mental health conditions
- Initiate and oversee collaborative research and clinical efforts on brain health both within the DoD and across other federal agencies, academia, and industry
- Participate in international research collaboration activities that address brain health issues.

## Expert Panels and SoS Meetings

The Brain Health Research Program has facilitated the PCO's ability to identify knowledge gaps and make research and clinical recommendations through participation in expert panels and attendance of SoS meetings. To support this effort, the Brain Health Program Coordinator attended scientific and medical conferences such as the Third Annual American Academy of Neurology (AAN) Sports Concussion Conference and the National Capital Area TBI Research Symposium in order to monitor cutting edge research developments and emerging research needs in the field of brain health. In addition, the Brain Health Research Program Coordinator represented the PCO on various scientific advisory boards and conference panels including the Medical Advisory Board for the General Electric (GE)-NFL Head Health Challenge, the scientific advisory board for the NCAA-DoD Grand Alliance: CARE Consortium, and the newly formed NFL scientific advisory board. The involvement in numerous conferences, advisory boards, and panels has enabled the Brain Health Research Program Coordinator to develop recommendations for research directions and clinical practice policies with the potential to close identified brain trauma related research gaps.

## Planning and Review Activities

Participation of the Brain Health Research Program Coordinator provided subject matter expertise in planning and review activities of DoD and external research programs further enabled the PCO to advise on TBI research gaps. The Brain Health Research Program Coordinator participated in review activities such as the Research and Analysis meeting for the TBI and Psychological Health Portfolios of the Joint DHP/VA/Department of Health and Human Services (DHHS) and IPR meetings of MOMRP/JPC-5 and Neuren Pharmaceuticals, an industry organization in collaboration with USAMRMC. The Brain Health Research Program Coordinator's role as a voting member on various review boards helps ensure that recognized blast injury knowledge gaps are



Photo credit: Brayton Metzger/US Navy

being addressed in current and future medical research programs. In addition, the Brain Health Research Program Coordinator is an active participant on the TED Government Steering Committee. He also serves on the planning committee for the 4<sup>th</sup> Federal Agency Conference on TBI. These interactions with other research organizations, both within and outside the DoD, have strengthened relationships and helped to identify future collaborations in the field of brain trauma research. Additionally, the Brain Health Research Program Coordinator serves on panels that review research protocols and may evaluate business practices submitted by internal and external organizations.

### Research Coordination

The Brain Health Research Program Coordinator represented the EA in the alignment of DoD TBI research activities with the NRAP. As a co-Primary Investigator for the CENC, a \$70 million consortium created in direct response to the NRAP, the Brain Health Research Program Coordinator directly supports the EA mission to coordinate DoD TBI research among DoD, VA and other organizations through communication, dissemination, and strategic planning activities. In this role, the Brain Health Research Program

helps Federal government organizations work more efficiently and effectively towards enhancing brain health research and improving clinical care.

### Collaborative Research and Clinical Efforts

The Brain Health Research Program Coordinator promotes collaboration by engaging with external organizations through neurotrauma related research and clinical activities. For instance, he represented USAMRMC at the ARL Cognition and Neuroergonomics Collaborative Technology Alliance Research Management Board review, presenting an overview of USAMRMC and fostering further collaboration. In addition, he attended numerous high impact meetings in the field of neuroscience including the Galveston Brain Injury Conference, the 34<sup>th</sup> Annual Symposium of the National Neurotrauma Society, and the Brain Trust Pathway to InnoVAtions meeting, forging relationships with researchers and clinicians from other federal government agencies, academic institutions, and industry organizations. Through these outreach and teaming efforts, the PCO facilitates collaboration essential to developing integrated research and clinical solutions to brain health needs.





## International Research Collaboration

The Brain Health Research Program Coordinator has continued to facilitate collaboration and bring awareness to brain trauma related research through involvement in international research endeavors. The Coordinator not only served as a panel leader at the International Brain Injury Association's 11<sup>th</sup> World Congress on Brain Injury, a congress attended by close to 1000 delegates from over 50 countries, but was also selected as an international TBI expert for the 5th International Consensus Conference on Concussion in Sport to be held in Berlin, Germany in early FY17. In support of this engagement, the Brain Health Research Program Coordinator performed a several month long scientific review for one of the 12 key topics and will serve as a panel member and member of the adjudication working group at the upcoming conference.

## JTAPIC Program

The JTAPIC Program was established at the USAMRMC in 2006 to assist the EA in fulfilling portions of its responsibilities under DoDD 6025.21E, in particular, the EA's responsibility to support the development, maintenance, and usage of a joint database for blast research-related information. The program's mission is to collect, integrate, analyze, and store operations, intelligence, materiel, and medical data to inform solutions that will prevent or mitigate injury during the full range of military operations, including blast injuries. The JTAPIC Program Management Office originally resided within the PCO, but it has since matured into a program of record.

The JTAPIC Program Management Office is located at Fort Detrick, Maryland, with partners throughout the US (see Table 2-2). It leverages the medical, intelligence, operational, and materiel expertise of these partnerships to support operational planning and the development of strategies to prevent or mitigate injuries during combat. The JTAPIC Program's key FY16 accomplishments are highlighted in Chapter 7.

**TABLE 2-2: JTAPIC Program Partners**

<b>Intelligence and Operational Partners</b>
National Ground Intelligence Center
Dismounted Incident Analysis Team
US Marine Corps Current Operations Analysis Support Team
Marine Corps Intelligence Activity
US Army Aeromedical Research Laboratory
<b>Medical Partners</b>
Armed Forces Medical Examiner System
Joint Trauma System
Naval Health Research Center
<b>Materiel/Acquisition Partners</b>
Project Manager, Soldier Protection Individual Equipment
Product Manager, Infantry Combat Equipment
US Army Research Laboratory

## Way Forward

The Commander, MEDCOM established the PCO to coordinate research efforts on behalf of the EA to advance prevention, mitigation, and treatment solutions for Service Members. In support of the EA's five Mission Thrust Areas, the PCO will continue to provide critical information on knowledge gaps in blast injury research sourced from collaborative efforts with scientists, clinicians, and engineers from across domestic and international blast injury RDT&E communities. For information on PCO activities in FY17 and beyond, see Chapter 8.

03



CHAPTER 3:

# NATO HUMAN FACTORS AND MEDICINE RESEARCH TASK GROUP

In FY16, the PCO participated in two NATO HFM (RTG) activities focused on blast injury. Explosive weapons are a significant and continuing source of casualties and injuries in NATO operations. Recent advances in PPE, in-theater medical care, and rapid evacuation are increasing survivability of blast encounters. Survivors of blast injuries commonly suffer from TBI, visual and auditory system injury, neurosensory damage, and extremity injuries resulting in amputation of the limb(s).

NATO advances blast injury research through S&T activities.

### S&T at NATO

The Science and Technology Organization (STO) is a NATO subsidiary body established to meet the collective S&T needs of NATO Nations and partner Nations. S&T activities embrace scientific research, technology development, transition, application and field-testing, experimentation and a range of related scientific activities that include systems engineering, operational research and analysis, synthesis, integration and validation of knowledge derived through the scientific method. NATO conducts these activities through two business models (see inset).

The Collaboration Support Office (CSO), one of three executive bodies within the STO, provides executive and administrative support to the activities conducted within the framework of NATO's collaborative business model. The CSO consists of six Technical Panels and one Group (Table 3-1) focusing on different S&T areas. Technical Panels and Groups, which drive S&T collaborative model activities, are made up of Technical Teams (TT) comprised of national representatives as well as renowned scientists, engineers and information specialists. In addition to providing critical technical oversight, the TTs provide a communication link to military users and other NATO bodies.

#### NATO SCIENCE & TECHNOLOGY BUSINESS MODELS

- 1. Collaborative:** NATO provides a forum where NATO Nations and partner Nations elect to use national resources to define, conduct, and promote cooperative research and information exchange
- 2. In-house delivery:** S&T activities conducted in a NATO dedicated executive body, having its own personnel, capabilities and infrastructure

The TTs conduct specific research activities of defined duration and format including task groups, workshops, symposia, specialists' meetings, lecture series, and technical courses.

The mission of the HFM Panel, one of the six CSO Technical Panels, is to provide the S&T base for optimizing health, human protection, well-being, and performance of the human in operational environments with consideration of affordability. This mission is accomplished by exchange of information, collaborative experiments and shared field trials and involves understanding and ensuring the physical, physiological, psychological and cognitive compatibility among military personnel, technological systems, missions, and environments.

Since April 2008, the PCO has participated in several HFM Panel activities related to blast injury. These activities sought to develop a

**TABLE 3-1: Six CSO Technical Panels and One Group**

Acronym	Name
AVT	Applied Vehicle Technology Panel
HFM	Human Factors and Medicine Panel
IST	Information Systems Technology Panel
SAS	System Analysis and Studies Panel
SCI	Systems Concepts and Integration Panel
SET	Sensors and Electronics Technology Panel
NMSG	NATO Modelling and Simulation Group



#### PREVIOUS NATO HFM ACTIVITIES RELATED TO BLAST INJURY

- HFM-090: Test Methodology for Protection of Vehicle Occupants against Anti-Vehicular Landmine Effects (2002–2006)
- HFM-175: Medically Unexplained Physical Symptoms in Military Health (2008–2012)
- HFM-193: Mild Traumatic Brain Injury in a Military Operational Setting (2009–2013)
- HFM-198: Injury Assessment Methods for Vehicle Active and Passive Protection Systems (2010–2013)
- HFM-207 Symposium: A Survey of Blast Injury across the Full Landscape of Military Science (2010–2012)

greater understanding of the mechanisms of blast injury and to translate scientific discoveries into prevention, mitigation, and treatment measures. In FY16, the PCO participated in two HFM RTGs, described below.

#### **HFM-234 (RTG): Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards**

Established in late 2012 with the PCO Director as the chair, the objective of HFM-234 (RTG) was to establish a framework for a new interdisciplinary research area focusing on the environmental toxicology of blast exposure. Previous discussion from HFM-207 Symposium highlighted research similarities between blast injury research and classic toxicology - in that both require an understanding of dose, mechanism of dose delivery, and dose-dependent endpoint. In consideration of these similarities, the purpose of the HFM-234 (RTG) was to address knowledge gaps by creating a systematic approach to better understand blast injuries. The HFM-234 (RTG) focused on standardizing animal models of blast injury; creating common methods for establishing

dose-response and route of exposure; generating computational models; specifying dose regimens relevant to human medical endpoints; and developing methods for translating basic research to medical products and/or improved PPE for Service Members. These focus areas were organized into five key deliverables:

- A comprehensive dictionary of blast injury terms
- Guidelines for conducting epidemiological studies of blast injury
- Guidelines for reproducing blast exposures in the laboratory
- Guidelines for using animal models in blast injury research
- Final Technical Report on HFM-234 activities.

The HFM-234 (RTG) TT was made up of 17 members from nine NATO member and partner Nations (see Figure 3-1). The HFM-234 (RTG) held six meetings hosted by different sponsoring nations over three years. The purpose of each meeting and its relationship to development of key deliverables is summarized in Table 3-2.

#### **Comprehensive Dictionary of Blast Injury Terms**

Recognizing the need for a common vocabulary of blast injury research terms to improve communication and facilitate cross-community collaboration, the HFM-234 TT developed the “Comprehensive Dictionary of Blast Injury Terms.” This dictionary provides a common vocabulary of terminology to improve information sharing and facilitate collaboration across diverse research communities and disciplines.

#### **Guidelines for Conducting Epidemiological Studies of Blast Injury**

Effective data collection and management is important for multisite epidemiological studies. Using frameworks established by the Institute of Medicine as well as other well-documented epidemiological protocols, the HFM-234 (RTG) developed the “Blast

Injury Epidemiological Study Guidelines” to standardize data collection, coding, and management, which will allow for cross-study comparisons and encourage greater international collaboration. The guidelines provide investigators with an epidemiologic framework and best practices for data collection. The guidelines also identify critical elements of a blast injury epidemiological study, including: a well-defined research question; a focused hypothesis; a detailed study protocol; logical sampling methodology; identification of biases and limitations; definition of all variables and study size; standardized survey instruments and operational procedures; and an analysis plan. The guidelines recommend an ethics review and documentation of measures taken to ensure data quality. By standardizing data collection and analysis of epidemiological studies of blast injury, these guidelines will enable international partners to more easily share data, compare outcomes, and collaborate on future multinational studies.

### Guidelines for Reproducing Blast Exposures in the Laboratory

As a part of the continuing effort to promote standardized study and data collection methodologies, the HFM-234 (RTG) developed guidelines to provide blast injury research laboratories with fundamental characteristics for collection and description of blast pressure waves. Consistent use of guidelines would allow for reliable comparisons to be made between studies with different laboratory settings, methods of blast wave generations, and types of blast injury.

### Guidelines for Using Animal Models in Blast Injury Research

These guidelines are intended to provide a framework for scientifically valid methodological approaches to address the pathological consequences of blast exposures, and assist researchers during all stages of blast trauma animal experiments. It is anticipated

**FIGURE 3-1: HFM-234 (RTG) Participating Nations**



that this will reduce inter-laboratory variability and allow valid comparisons of results. They are not intended to be overly prescriptive but the aim is to ensure that experiments can be validated and replicate the human condition to enable the translation of results.

**TABLE 3-2: HFM-234 (RTG) Program of Work**

Activity Workshop	Month/Year	Purpose	Host/Location
Meeting 1	1–2 Jul 2013	HFM-234 (RTG) Kick-off	STO (Paris)
Comprehensive Dictionary of Blast Injury Terms	Ongoing	Develop a dictionary of commonly used terms with definitions	Canada (Virtual)
Meeting 2	10–12 Dec 2013	Develop recommendations for collecting data necessary for conducting epidemiological studies	USA (Fort Detrick, Maryland)
Meeting 3	21–23 May 2014	Develop guidelines to reproduce blast exposure conditions in the laboratory	Canada (Medicine Hat, Alberta)
Meeting 4	7–9 Oct 2014	Synthesize workshops, discuss computational modeling, and review dictionary	Estonia (Tallinn)
Meeting 5	12–14 May 2015	Develop recommendations for standardized animal models and a roadmap for dose-dependent curves	Sweden (Stockholm)
Meeting 6	19–21 Jan 2016	Review, amend and agree the five group deliverables	England (Salisbury, Wiltshire)

### **HFM-270 (RTG): Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-related Threats**

To build upon progress made by the HFM-207 Symposium and HFM-234 (RTG), which highlighted requirements for biomedically-valid computational models and simulation of blast injury that incorporate both biomechanical and physiological responses, the PCO proposed a new RTG leveraging previous, ongoing, and planned blast injury biomedical research and computational modeling efforts among the participating nations. This HFM RTG proposal was approved by the NATO STO in late 2015 and was designated HFM-270 (RTG) with the kickoff meeting scheduled for October 2016 and culminating with the final report due in 2019. The objective of this RTG is to develop a framework for translating scientific information into the capability to model the mechanisms of

human lethality, injury, and impairment across the spectrum of blast-related threats. This framework will provide guidelines, identify gaps and make recommendations for the validation of effective modeling and simulation capabilities. When tightly coupled to biomedical research data, modeling and simulation has the potential to elucidate tissue level mechanisms of blast injury needed to design and test protection systems for individuals. Table 3-3 describes the topics to be covered by HFM-270 (RTG). The PCO Director will chair this RTG comprised of SMEs from the US, Canada, France, Germany, Israel, Japan, Netherlands, New Zealand, Sweden, Turkey, and the United Kingdom. The Program of Work will be finalized in early FY17 at the kickoff meeting. The deliverables to be developed by this RTG are expected to parallel those of HFM-234 (RTG) but focus on modeling and simulation capabilities related to blast injury.



**TABLE 3-3: HFM-270 (RTG) Topics**

The HFM-270 (RTG) will develop the framework for creating and evaluating effective systems that protect Service Members from blast-related threats. The topics to be covered include the following:

- Computational modeling of human lethality, injury, and impairment from blast threats, in both mounted and dismounted scenarios
- Previous, ongoing, and planned blast injury biomedical research and computational modeling efforts, and how these fit into overarching frameworks for understanding mechanisms of injury and development of protective systems
- Identification of the gaps that remain in the mechanisms of blast-related injury and in understanding how to adequately protect from these injuries
- Survey of blast lethality, injury, and impairment research infrastructure and identification of cross-NATO research opportunities



Photo credit: US Air Force

## Way Forward

Advancements in blast injury prevention and treatment for Service Members require close collaboration between researchers, clinicians, engineers, and other stakeholders both domestic and internationally. By developing official NATO documents to standardize how data are collected, coded, and analyzed, the HFM-234 (RTG) is lifting the barriers to cross-study comparison with the publication of the guidelines for conducting epidemiological studies of blast injury, dictionary of blast injury terms, guidelines for reproducing blast exposures in the laboratory, and guidelines for using animal models in blast injury research.

As a part of the continuing NATO effort, the new HFM-270 (RTG) will focus on developing a framework for translating scientific information into the capability to model the mechanisms of human lethality, injury, and impairment across the spectrum of blast-related threats and potentially reduce the time required to develop and field effective blast injury protection systems.



04

CHAPTER 4:

# MHS BLAST INJURY PREVENTION STANDARDS RECOMMENDATION PROCESS



**D**oDD 6025.21E assigns to the EA the responsibility to “Provide medical recommendations with regard to blast-injury prevention, mitigation, and treatment standards to be approved by the ASD(HA).” The term, “MHS Blast Injury Prevention Standard,” is defined as a “biomedically-valid description of the physiologically- or biomechanically-based injury and performance response of a human to blast insults.” The standards can range from simple dose-response curves and injury thresholds that address single components of blast insults, such as peak force, to complex algorithms and computational models that address multiple components of blast insults, such as force-time history. Candidate standards include injury thresholds, human injury probability curves, and injury prediction tools needed to generate the information for informed trade-off and risk acceptance decisions by appropriate decision makers in the RDT&E, medical, and operational Stakeholder communities across the DoD Components. These standards support weapon system health hazard assessments, combat platform occupant survivability assessments, and protection system development and performance testing (Figure 4-1).

Designed to address the above requirement, the MHS BIPSR Process is the DoD’s first unbiased, inclusive, stakeholder-driven process designed to identify and assess the suitability and applicability of existing candidate standards and

to recommend standards that meet DoD Stakeholder needs with a suitable level of validity, rigor, precision, and confidence.

The BIPSR Process has two major objectives. The first is to identify existing biomedically-valid candidate standards for immediate use by the DoD. The second is to inform the research community of gaps where no suitable candidate standards exist. The BIPSR Process is not a research program and does not develop new candidate standards. The Process does not attempt to impose acceptability or survivability requirements on the Stakeholder communities; rather, it seeks to ensure that the DoD uses the best available, scientifically sound, and biomedically-valid standards that will protect our Service Members from blast injuries.

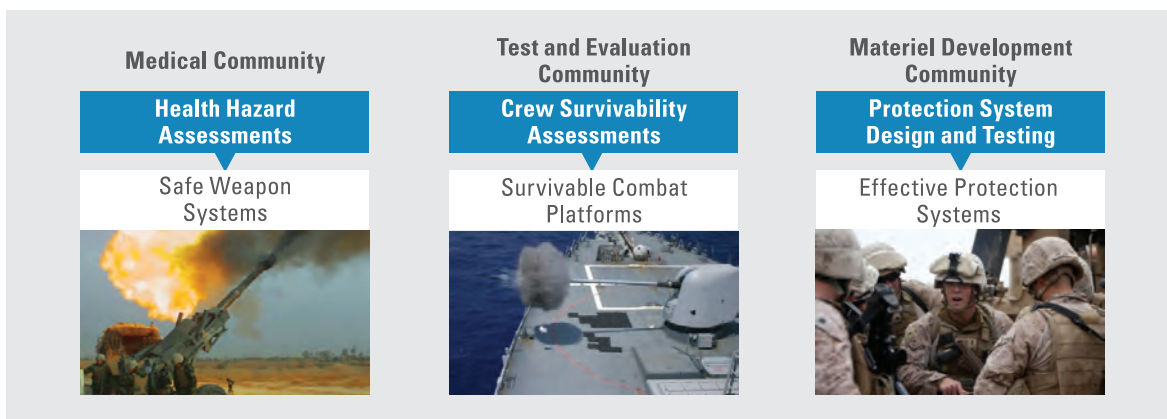


### The BIPSR Process

The BIPSR Process is designed to identify and objectively evaluate the details of available blast injury prevention standards to determine their suitability for use by the DoD in health hazard and survivability assessments, as well as protection system development. The BIPSR Process can be tailored for a specific mechanism of injury, resulting in an objective set of recommendations that can serve as the basis of a medical standard.

The BIPSR Process is designed to identify and critically evaluate blast injury prevention candidate standards and to recommend those

**FIGURE 4-1: Blast Injury Prevention Standards Framework**





that would best serve as MHS Blast Injury Prevention Standards to inform the DoD medical, test and evaluation (T&E), materiel development (MATDEV), and operational communities.

Core elements of the BIPSR Process include:

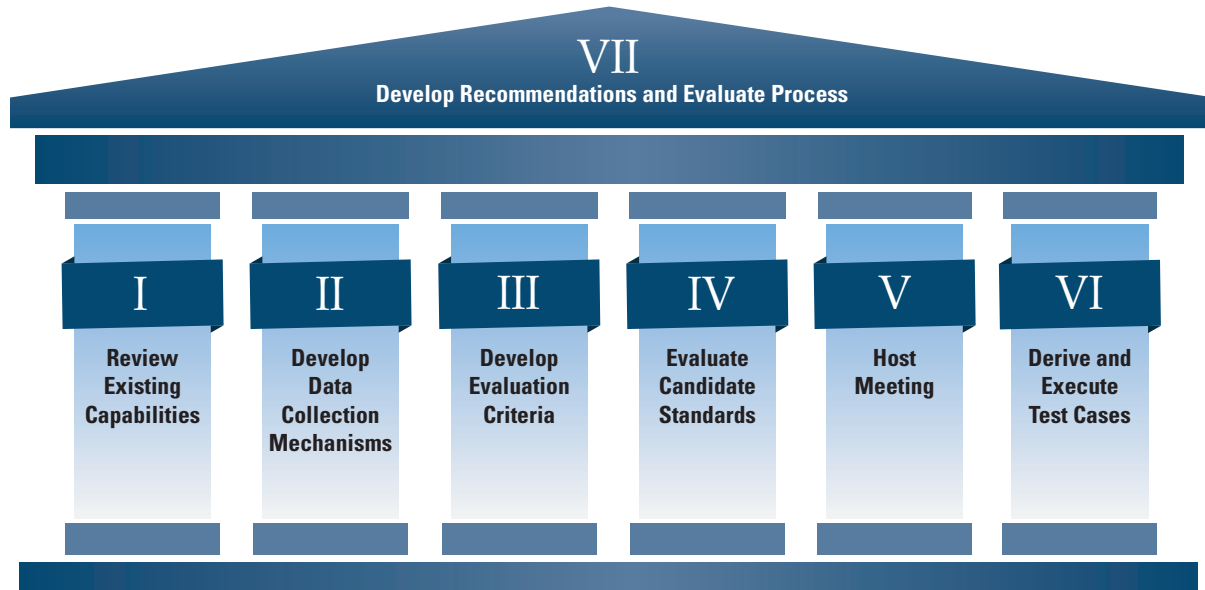
- **BIPSR Process Stakeholders Committee:** Defines the problem statement and scenarios to be assessed, identifies gaps in the current standard set, drives implementation, and participates in all major decisions throughout all phases of the BIPSR Process.
  - **Focused Stakeholder Committee:** A subset of BIPSR Process Stakeholders with expertise related to a particular Blast Injury Type. They review existing capabilities to include a literature survey using relevant keywords, identify SMEs, identify existing candidate standards, define intended uses, and identify gaps.
- **SME Panel:** A broad-based, non-advocacy panel whose members are drawn from industry, academia, and government. The SMEs have experience in the domain of interest, development of the candidate standard product (e.g., dose-response curve, computational model), T&E, clinical medicine, and Independent Verification and Validation.
- **Stakeholder Driven Consensus-Building Meeting:** A forum for Stakeholders, the SME Panel, users, analysts, and candidate standard developers to discuss the DoD's intended uses, gaining context and scope for the evaluation, and allowing for individual interviews with developers to gain a detailed understanding of candidate standard capabilities and/or profiles.

The BIPSR Process is initiated by a literature review that serves two purposes: (1) to identify existing capabilities and standards pertinent to the injury under evaluation, and (2) to compile a list of appropriate SMEs who may serve on the SME Panel performing the evaluations. Once a list of candidate standards has been defined, the iterative nature of the BIPSR Process builds layers of information about the capabilities of each candidate under consideration. The SME Panel conducts the initial evaluations, giving balanced, objective, and knowledgeable advice on the candidate standard's suitability for the DoD's intended uses based on the available information. The list of candidate standards is narrowed based on an evaluation against a set of defined criteria. Information generated through the evaluation process serves as the basis for a meeting that provides a forum for Stakeholders (users, analysts, and developers) to build consensus, share information, and discuss the applicability of a candidate standard to the DoD's intended use—potentially narrowing the list of candidates that move forward in the evaluation process. In some cases (e.g., for computational models), the candidate standards undergo a detailed examination of capabilities through a rigorous test process focused on Stakeholder-defined test scenarios. Once the test cases have been run, the results are assessed using statistical tools. In the final step of the BIPSR Process, the non-advocacy SME Panel and MITRE team conduct final evaluations, develop standards recommendations, and prepare process improvement recommendations.

Collaboration opportunities are integrated across the BIPSR Process. As depicted in Figure 4-2, the BIPSR Process consists of seven fundamental subprocesses represented by six pillars supporting an overarching process.

The BIPSR Process is designed to leverage the information from the previous phases,

**FIGURE 4-2: BIPSR Process Pillars**



which builds layers of information about the viability of the candidate standards. As a result, the latter subprocesses (V and VI) do not necessarily occur in sequence but are iterated as necessary to produce sufficient information to support the recommendations. Table 4-1 contains a high-level description of various activities that take place in the subprocesses that make up the BIPSR Process.

The timeline associated with implementation of the BIPSR Process is driven by the number of candidate standards identified, the complexity of the candidate standards, and the complexity of the injury type. The BIPSR Process can be tailored to support compressed, quick turnaround implementation that meets the need and critical nature of specific injury types.

**TABLE 4-1: BIPSR Process Pillar Activities**

No.	Subprocess	Activities
I	Review Existing Capabilities	<ul style="list-style-type: none"> <li>Engage Stakeholders and identify relevant standards for the injury criteria through a systematic literature survey</li> <li>Establish a broad-based, independent review panel</li> <li>Poll the community by issuing a RFI</li> </ul>
II	Develop Data Collection Mechanisms	<ul style="list-style-type: none"> <li>Develop standardized evaluation and information templates</li> <li>Conduct frequent panel meetings to establish review criteria</li> </ul>
III	Develop Evaluation Criteria	<ul style="list-style-type: none"> <li>Define scenarios and evaluation metrics</li> <li>Hold a consensus-building meeting</li> </ul>
IV	Evaluate Candidate Standards	<ul style="list-style-type: none"> <li>Conduct an interactive set of evaluations with the SME Panel and developers</li> </ul>
V	Host Meeting	<ul style="list-style-type: none"> <li>Hold a consensus-building meeting for Stakeholders to share information</li> </ul>
VI	Derive and Execute Test Cases	<ul style="list-style-type: none"> <li>Involve users and Stakeholders in the development of scenario-based test cases and execute the tests for the identified candidate standards (where applicable)</li> </ul>
VII	Develop Recommendations and Evaluate Process	<ul style="list-style-type: none"> <li>Produce a report that recommends standards for PCO consideration as the basis for MHS Blast Injury Prevention Standards</li> <li>Recommend improvements to the BIPSR Process</li> </ul>



Photo credit: PFC Daniel Parrott/US Army

The identification and prioritization of the injury mechanisms fall outside the scope of the BIPSR Process, and is the responsibility of the PCO and BIPSR Process Stakeholders. The BIPSR Process identifies but does not resolve capability gaps in the current standards; these gaps are shared with the DoD medical and non-medical S&T communities.

The PCO developed the BIPSR Process via a series of BIPSR Process Stakeholders meetings, and obtained ASBREM Committee approval. The Johns Hopkins University Applied Physics Laboratory (JHU/APL), a University Affiliated Research Center and DoD trusted agent, supported the PCO through the piloting of the BIPSR Process with an evaluation and analysis of the Toxic Gas Inhalation as an exemplar. Currently, the MITRE Corporation, a DoD trusted agent that operates FFRDCs, supports the PCO in the execution of the BIPSR Process by working closely with BIPSR Process Stakeholders and SMEs in the blast community.

## BIPSR Process Improvements

Seeking to expedite the timeline required for evaluation of MHS BIPSR Process Blast Injury Type, the PCO developed the BIPSR Process simulation model using the Business Process Modeling Notation (BPMN) standard. This standard business process modeling methodology graphically represents the BIPSR Process activities and facilitates quantitative and qualitative analysis via simulation.

The BPMN model was populated with the actual timeline for the Lower Extremity BIPSR Process, resulting in confidence that the model is accurate. The PCO evaluated multiple scenarios for process improvements and recommended a revised BIPSR Process, which received concurrence in the January 2015 BIPSR Process Stakeholder meeting. These revisions are projected to accelerate the timeline for completion of all MHS BIPSR Process Blast Injury Types by several years.

A key change in the revised BIPSR Process is reordering the sequence of preliminary activities. Specifically, performing a literature search and interviewing SMEs early on allows the PCO to develop an understanding of existing capabilities prior to defining Stakeholder requirements. Understanding the existing research for an MHS BIPSR Process Blast Injury Type earlier in the process ensures that a common context and terminology set are established prior to engagement of the Stakeholders for requirements definition, effectively improving the efficiency of Stakeholder interactions.

On the basis of BPMN analysis, a process step was also added to the BIPSR Process for cases in which a gap in standards is identified. This step allows for defining how to disseminate the gap information to the research community and permits the close out of the BIPSR Process upon declaration of a gap, rather than continue through the entire BIPSR Process. Overall, the process revisions to the BIPSR Process are projected to reduce the time required to declare a gap for each blast injury type.

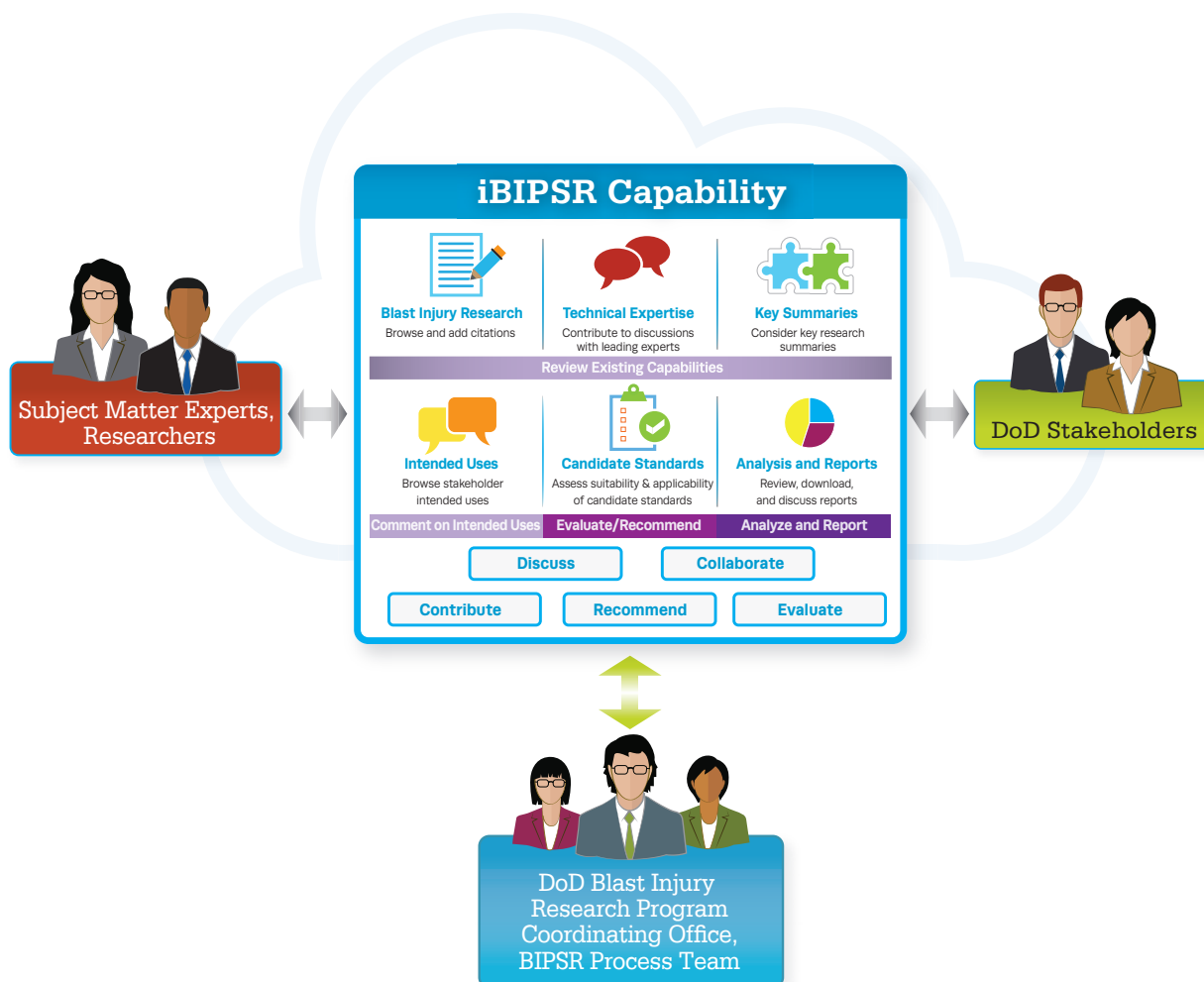


In addition, the development and implementation of a web-based collaboration environment known as Interactive Blast Injury Prevention Standards Recommendation (iBIPSR) was initiated to enhance information sharing in real time and to further reduce the timeframe to complete the BIPSR Process for each of the remaining MHS BIPSR Process Blast Injury Types.

### iBIPSR Capability

The iBIPSR capability has foundations in collaborative semantic web technology, an information synthesis technology well suited for large, collaborative, multi-user information sharing and decision making efforts. The complete development of the iBIPSR site is expected to enhance information sharing among blast injury experts and support the PCO's EA mission to leverage existing knowledge and foster collaboration among academia, industry, international partners, and government

**FIGURE 4-3: BIPSR Process Supported by the iBIPSR Site**



organizations by providing a platform for continuous collaboration throughout the BIPSR Process.

As shown in Figure 4-3, the iBIPSR capability supports a variety of users with planned collaborative interactions between and among Stakeholders, SMEs, the PCO, and the MITRE team. Additionally, the iBIPSR capability offers transparency by capturing and managing Stakeholder organizations' knowledge gaps and needs, and it facilitates understanding through near-real-time communication among participants. iBIPSR is an evolving capability. The MITRE team is proving out the iBIPSR capability through the Auditory Blast Injury Type and enhancing the iBIPSR capability by incorporating feedback and suggestions received from the Auditory Focused Stakeholder Committee members.

### Power of iBIPSR

The iBIPSR capability represents a novel way to reduce the timeline of the BIPSR Process without sacrificing decision quality (Table 4-2). Following initial enrollment of the Auditory Focused Stakeholders, the iBIPSR capability has been improved by expanding the user base and dynamically incorporating user feedback to develop and improve site features. Ultimately, the PCO anticipates that all BIPSR Process Stakeholders and designated SMEs will use the iBIPSR capability.

## BIPSR Process Stakeholder Meeting

The PCO hosted a BIPSR Process Stakeholders Meeting to present progress and recommendations for the Blast Injury Types in progress. During the meeting, the MITRE team: (1) presented the detailed activities and outcomes of the Focused Stakeholder meetings, highlighting findings and conclusions for the Lower Extremity, Spine and Back, and Upper Extremity Blast Injury Types (for details

**TABLE 4-2: The Power of the iBIPSR Site**

The iBIPSR site is well-suited to large, collaborative, multi-user information sharing and decision making:

- Leverages existing knowledge
- Utilizes technology to foster continuous collaboration
- Removes obstacles to participation (e.g., travel and scheduling)
- Allows for broad engagement in the process with access to information used in all stages of the BIPSR Process

see subsequent chapter sections); (2) shared progress on iBIPSR capability development, including plans to provide iBIPSR website access to all BIPSR Process Stakeholders; and (3) provided information regarding the reprioritization effort underway to rank order the nine remaining MHS BIPSR Process Blast Injury Types to align with the current and future needs of the DoD. Twenty-nine Stakeholders representing the Army, Navy, Air Force, and Marine Corps operational, medical, T&E, and MATDEV COIs participated in the meeting.

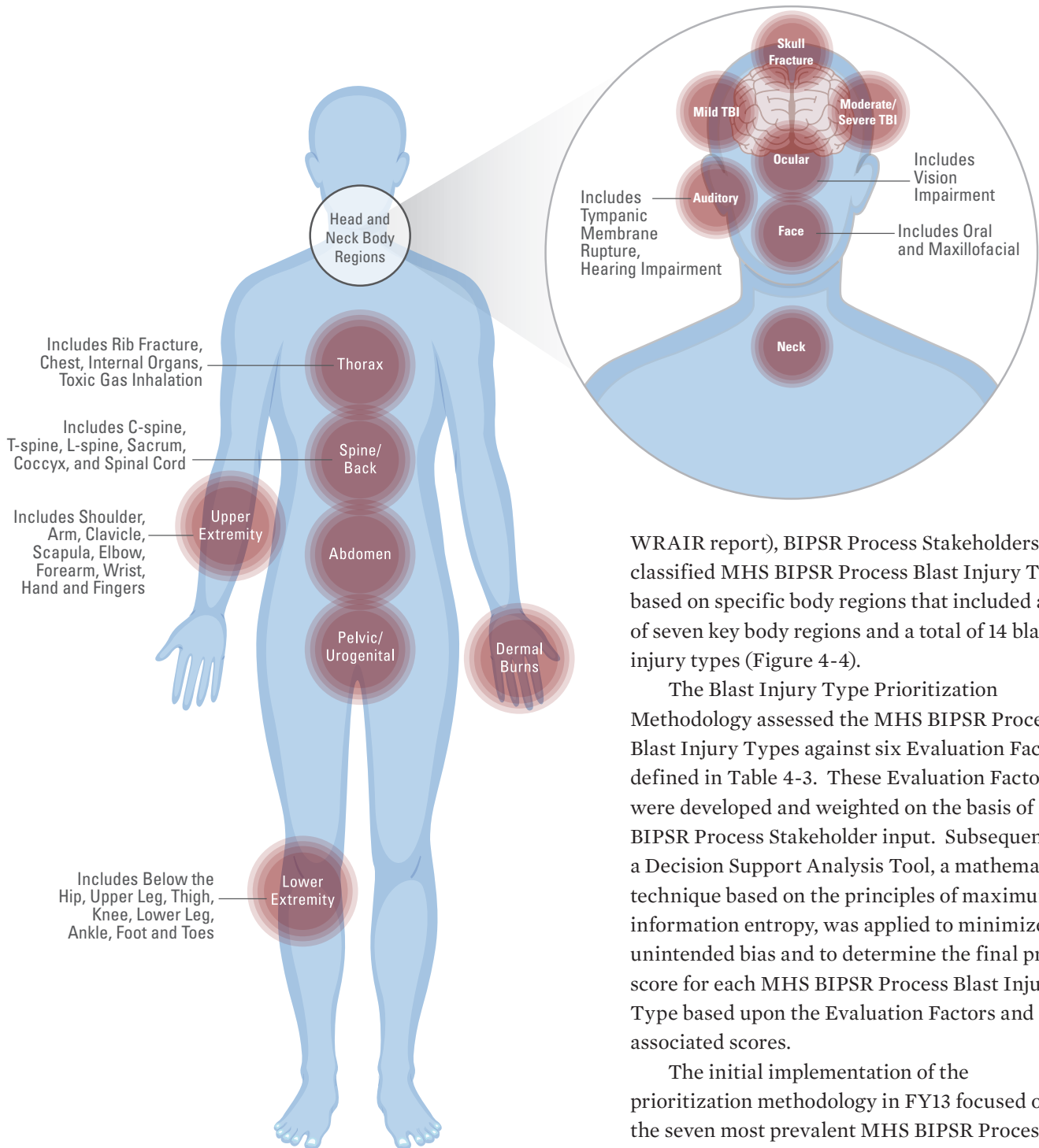
### Next Steps

The MITRE team plans to continue proving out the iBIPSR capability using the Auditory Blast Injury Type as an exemplar, complete the reprioritization effort for the remaining MHS BIPSR Process Blast Injury Types, and initiate the BIPSR Process for the Dermal Burns Blast Injury Type. The PCO plans to hold the next BIPSR Process Stakeholders Meeting in FY17.

## MHS BIPSR Process Blast Injury Type Prioritization

Through a series of BIPSR Process Stakeholders Committee meetings hosted by the PCO in FY13, BIPSR Process Stakeholders classified 14 MHS BIPSR Process Blast Injury Types based on specific body regions. Figure 4-4 shows the categorization of MHS BIPSR Process Blast Injury Types.

**FIGURE 4-4: Categorization of MHS BIPSR Process Blast Injury Types by Body Region**



The PCO developed a methodology to establish a priority ranking across the MHS BIPSR Process Blast Injury Types, which have been defined by consensus among BIPSR Process Stakeholders. Shifting from an older classification of injury types that referred to individual organs and bones (as described in a 1989

WRAIR report), BIPSR Process Stakeholders classified MHS BIPSR Process Blast Injury Types based on specific body regions that included a total of seven key body regions and a total of 14 blast injury types (Figure 4-4).

The Blast Injury Type Prioritization Methodology assessed the MHS BIPSR Process Blast Injury Types against six Evaluation Factors defined in Table 4-3. These Evaluation Factors were developed and weighted on the basis of BIPSR Process Stakeholder input. Subsequently, a Decision Support Analysis Tool, a mathematical technique based on the principles of maximum information entropy, was applied to minimize unintended bias and to determine the final priority score for each MHS BIPSR Process Blast Injury Type based upon the Evaluation Factors and associated scores.

The initial implementation of the prioritization methodology in FY13 focused on the seven most prevalent MHS BIPSR Process Blast Injury Types: mTBI, Moderate to Severe TBI, Auditory, Abdomen, Cervical Spine, Lower Extremity, and Upper Extremity. Through this initial prioritization effort, the Lower Extremity Blast Injury Type was identified as the highest priority MHS BIPSR Process Blast Injury Type to be evaluated using the BIPSR Process.





**TABLE 4-3: BISPR Process Evaluation Factors**

Evaluation Factors	Description
Impact on Operational Readiness	The time for a Service Member to return to duty.
Blast Injury Prevalence Rate	The number of cases of a given Blast Injury Type expressed as a percentage of the total number of blast injuries.
Treatment Resources	Roles of medical treatment, which are the distribution of medical resources and capabilities to provide Service Member's medical care.
Maturity of the Science	Determined by the existence of established standards (e.g., Military Standard (MIL-STD)-1474D Noise limits design criteria) or, in the absence of established standards, by the degree to which biomedically-valid injury mechanisms have been published in the peer-reviewed scientific literature, or by the development and application of assessment methodologies based on the established injury mechanisms to assess injury risks.
Rehabilitation Resources	Resources required to support a Service Member's rehabilitation beyond immediate treatment resources and may include therapy, pharmaceuticals, or devices needed to reset for QOL.
Disability Percentage	Designated percentage assigned to an injury type when calculating disability benefits.

To date, Lower Extremity, Spine and Back, and Upper Extremity Blast Injury Types have gone through the BISPR Process, with final reports completed or in progress; the BISPR Process has been initiated for Auditory and Dermal Burn Blast Injury Types utilizing the iBISPR capability.

The PCO has initiated a reprioritization effort for the remaining nine MHS BISPR Process Blast Injury Types: Ocular, Face, Neck, Thorax, Abdomen, Pelvic/Urogenital, Skull Fracture, mTBI, and Moderate to Severe TBI to ensure that the current needs of the operational environment and the DoD are being met. The reprioritization effort applies an established mathematical analysis technique, Multi-Attribute Utility Theory (MAUT), a widely used, widely accepted methodology for guiding tradeoffs among multiple objectives. In the past, MAUT

has been used, for example, in the Army's 2005 Base Realignment and Closure process, in a National Research Council evaluation of plans for protecting the population from the effects of a nuclear incident, and in selecting a portfolio of solar energy projects for the Department of Energy.

#### **Next Steps**

This reprioritization effort will assess the MHS BISPR Process Blast Injury Types against the six BISPR Process Evaluation Factors (Table 4-3) involving the BISPR Process Stakeholders input to rank order the remaining nine MHS BISPR Process Blast Injury Types.



## Update on Implementation of the BIPSR Process for MHS BIPSR Process Blast Injury Types

### Implementation of the BIPSR Process for the Spine and Back Blast Injury Type

The PCO hosted the second Spine and Back Focused Stakeholders Committee Meeting in which the MITRE team presented progress, findings, and recommendations. This Meeting resulted in the Focused Stakeholder Committee declaring a knowledge gap for the Spine and Back Blast Injury Type, and recommending the following key findings:

- None of the existing criteria are suitable for use as a DoD Blast Injury Prevention Standard
- Research on spine and back injury to date comes largely from the automotive and aviation industries, where the physical phenomena in these hazard environments show some overlap with the blast phenomena encountered by Service Members
- Validated injury criteria are lacking for female Service Members
- Existing research is limited to vehicle-mounted conditions, with few studies on dismounted conditions

#### Next Steps

The MITRE team is in the process of preparing the final report.

### Implementation of the BIPSR Process for Upper Extremity Blast Injury Type

The PCO hosted the second Upper Extremity Focused Stakeholders Committee Meeting in which the MITRE team presented progress, findings, and recommendations. This Meeting resulted in the Focused Stakeholder Committee declaring a knowledge gap for the Upper Extremity Injury Type, and recommending the following key findings:

- None of the existing criteria are suitable for use as a DoD Blast Injury Prevention Standard

- Any comprehensive standard for upper extremity blast injury protection would have to predict injury to multiple parts of the upper extremity, including fractures of the long bones, and soft tissue injuries especially at the shoulder, hand, and wrist, each of which has its own vulnerabilities
- Soft tissue vulnerabilities can be as severe or more severe than bony fractures, and require detailed study under a blast environment construct

#### Next Steps

The MITRE team is in the process of preparing the final report.

### Implementation of the BIPSR Process for the Auditory Blast Injury Type as an Exemplar for enhancing the iBIPSR Capability

The BIPSR Process for the Auditory Blast Injury Type is in progress and is being used to prove out the iBIPSR capability. Following the initial steps of the BIPSR Process, the Existing Capabilities Review of the Auditory Blast Injury Type included establishing the Auditory Focused Stakeholder Committee, performing a literature survey, posting an RFI on Federal Business Opportunities, and interviewing eight SMEs from industry, academia, and government agencies.

The PCO hosted the first meeting of the Auditory Focused Stakeholder Committee in which the MITRE team presented progress on the findings of the Existing Capabilities Review and obtained feedback on the literature survey findings and the requirements definition approach. Following this first Committee Meeting, the MITRE team interviewed 15 Auditory Focused Stakeholders from 12 organizations, representing all four Services and the VA, and representing the medical, operational, MATDEV, and T&E COIs. These one-on-one Stakeholder interviews collected information through a series of questions designed to capture information about what





Photo credit: Brayton Metzger/US Navy

is driving the standard requirements. The questions were aimed at determining the operational needs for MHS BIPSR Process Blast Injury Prevention Standards, the level of biofidelity needed for validation of the injury models, and the priorities for different aspects of auditory blast injury prevention. In addition, questions were asked regarding the general aspects of the current state of auditory injury prevention and the ideal format for the blast injury standard. The MITRE team is in the process of compiling the information gained

from these interviews, the Existing Capabilities Review, RFI submissions, SME interviews, and Auditory Focused Stakeholder feedback.

### **Next Steps**

The MITRE team is in the process of preparing the draft report capturing outcomes of the Existing Capabilities Review for presentation at the second Auditory Focused Stakeholder Committee meeting, planned for October 2016. In addition, the MITRE team plans to continue developing the iBIPSR capability.

### **KEY ACCOMPLISHMENTS**

- Completed the BIPSR Process evaluation for the Spine and Back and Upper Extremity Blast Injury Type
- Initiated implementation of iBIPSR capability by providing access to BIPSR Process Stakeholders
- Started proving out the iBIPSR capability, using the Auditory Blast Injury Type as an exemplar

### **Way Forward**

In the coming year, the PCO plans to complete the BIPSR Process for the Spine and Back and Upper Extremity Blast Injury Types, prove out the iBIPSR capability using the Auditory Blast Injury Type as exemplar, initiate execution of the Dermal Burn Blast Injury Type, and continue the reprioritization of the remaining MHS BIPSR Process Blast Injury Types. The PCO anticipates enhancing the iBIPSR capability to identify the best available scientifically sound candidate standards to protect Service Members from the entire spectrum of blast injuries.



05



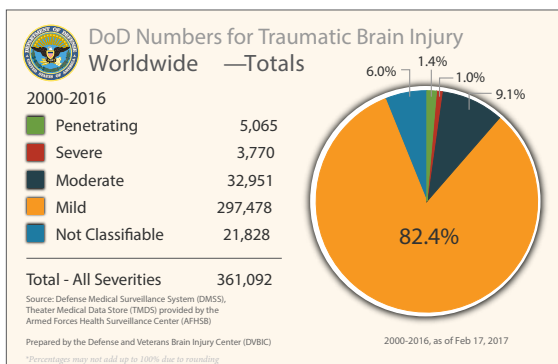
CHAPTER 5:

# BLAST-RELATED TRAUMATIC BRAIN INJURY



**T**BI, one of a wide array of injuries that can result from explosive blast exposure, poses a significant health concern for US military Service Members. Since 2000, more than 340,000 Service Members have sustained a TBI (see Figure 5-1). Decades of research by military and civilian healthcare experts have revealed that TBI can result in long-term consequences requiring sustained follow-up care.<sup>5,6,7</sup>

**FIGURE 5-1: Total TBIs Sustained Worldwide by US Service Members**



Blast-related TBI can result from exposure to explosions, including those caused by bombs, grenades, land mines, mortar/artillery shells, and IEDs. A blast-related TBI can occur when atmospheric pressure changes from the blast shockwave impact the brain, when flying objects such as shrapnel penetrate the head and brain, or when the blast sends bodies into motion causing the head to hit an object such as the ground or inside of a vehicle; these injuries are referred to as primary, secondary, and tertiary TBIs, respectively.<sup>8,9</sup> While the pathophysiology of secondary and tertiary blast-related TBI is thought to resemble injuries sustained in civilian settings (e.g., falls and motor vehicle collisions), many knowledge gaps persist, particularly in reference to primary blast-related TBIs. Furthermore, much is unknown regarding TBI diagnosis and outcomes; whether blast-related TBI differs from civilian TBI, how the different types of blast-related TBI affect individuals, and the relationship between

blast-related TBI and PTSD have not yet been clearly elucidated.<sup>10</sup>

Blast-related TBI has been increasingly common during recent conflicts, including OEF, OIF, and Operation New Dawn. Over 60 percent of combat injuries sustained during OEF/OIF are due to explosive blast exposure.<sup>11</sup> Although the majority of TBIs in Service Members occur in non-deployed settings such as during trainings or participation in sports and leisure activities, blast-related TBI and polytrauma are increasingly recognized as issues that directly affect the individual health of Service Members as well as subsequent unit readiness, resilience, and troop retention.

The DoD has worked for decades to address health concerns associated with both blast- and nonblast-related TBI in Service Members. TBI research and care provided by the DoD is enhanced and coordinated by the DCoE through the Defense and Veterans Brain Injury Center (DVBIC), which is its operational component center.<sup>7</sup> DCoE and DVBIC serve essential roles in the promotion of research, clinical care, and educational services and resources for Service Members with blast-related TBI.

## DCoE

The mission of DCoE is to improve the lives of Service Members, Veterans, and their Families by advancing excellence in psychological health and TBI prevention and care. DCoE identifies knowledge and materiel gaps, prioritizes research needs, and translates research findings into clinical practice to improve patient outcomes. By integrating state of the science knowledge and information regarding psychological health and TBI, DCoE strives to ensure that the DoD meets the needs of the Nation's Military communities, Service Members, and Families. DCoE also promotes psychological health and TBI care practices and policies across the Services by leading numerous collaborative efforts, including those between the VA, other federal agencies, civilian agencies, community leaders, advocacy groups, clinical experts, and academic



institutions dedicated to advancing scientific knowledge regarding psychological health and TBI.

Congress established DCoE in 2007 to enhance Military readiness and resilience through prevention, screening, diagnosis, treatment, recovery, and reintegration efforts.<sup>12</sup> In 2016, DCoE became a division of the DHA Healthcare Operations Directorate. As such, DCoE contributes to the integrated combat support the DHA provides to the MHS.

### DCoE Structure and Capabilities

Operating as an integrated group of experts, DCoE oversees three centers (Table 5-1) that contribute unique insights, standards, clinical tools, and research products to the fields of psychological health and TBI.<sup>13</sup>

## DVBIC

The mission of DVBIC is to serve active duty Service Members, their beneficiaries, and Veterans with TBI through state of the science clinical care, innovative clinical research initiatives and educational programs, and by supporting force health protection services.<sup>14</sup> DVBIC's activities include assisting the briefing of Service Members prior to deployment, the screening of Service Members upon return from deployment, provider training at Military treatment facilities (MTFs), data gathering and analysis mandated by Congress and the DoD, and advancing the field of TBI care through innovative research programs.

### DVBIC History: 25 Years of Service

Mandated by Congress in 1991, DVBIC launched in 1992 as the Defense and Veterans Head Injury Program in response to the first Gulf War and the increased need to treat Service Members and Veterans with TBI.<sup>15</sup> As a result, DVBIC became the first DoD entity with the primary goal of ensuring that Service Members and Veterans with TBIs receive the specialized care they require, including their appropriate evaluation, treatment, and follow-up. Since DVBIC's launch, the principle of "learn as we treat" has guided the agency's approach to TBI research, clinical care,

prevention and education. Highlights of how DVBIC has achieved this goal over the past two and a half decades are described in Figure 5-2.<sup>16</sup>

### DVBIC Structure and Capabilities

DVBIC is headquartered in Silver Spring, Maryland, where oversight, administrative, and infrastructure functions are performed. DVBIC maintains 17 network sites at MTFs and VA medical centers, integrating specialized TBI care, research, education, and training across the DoD and VA. DVBIC strives to meet its mission by providing TBI thought leadership, managing the DoD's TBI Pathway of Care, and engaging in research, clinical, and educational activities throughout its network of sites.

### Thought Leadership

DVBIC's accomplishments and ongoing contributions reflect the experience and strength of the organization's leadership, particularly with regards to research, care management,

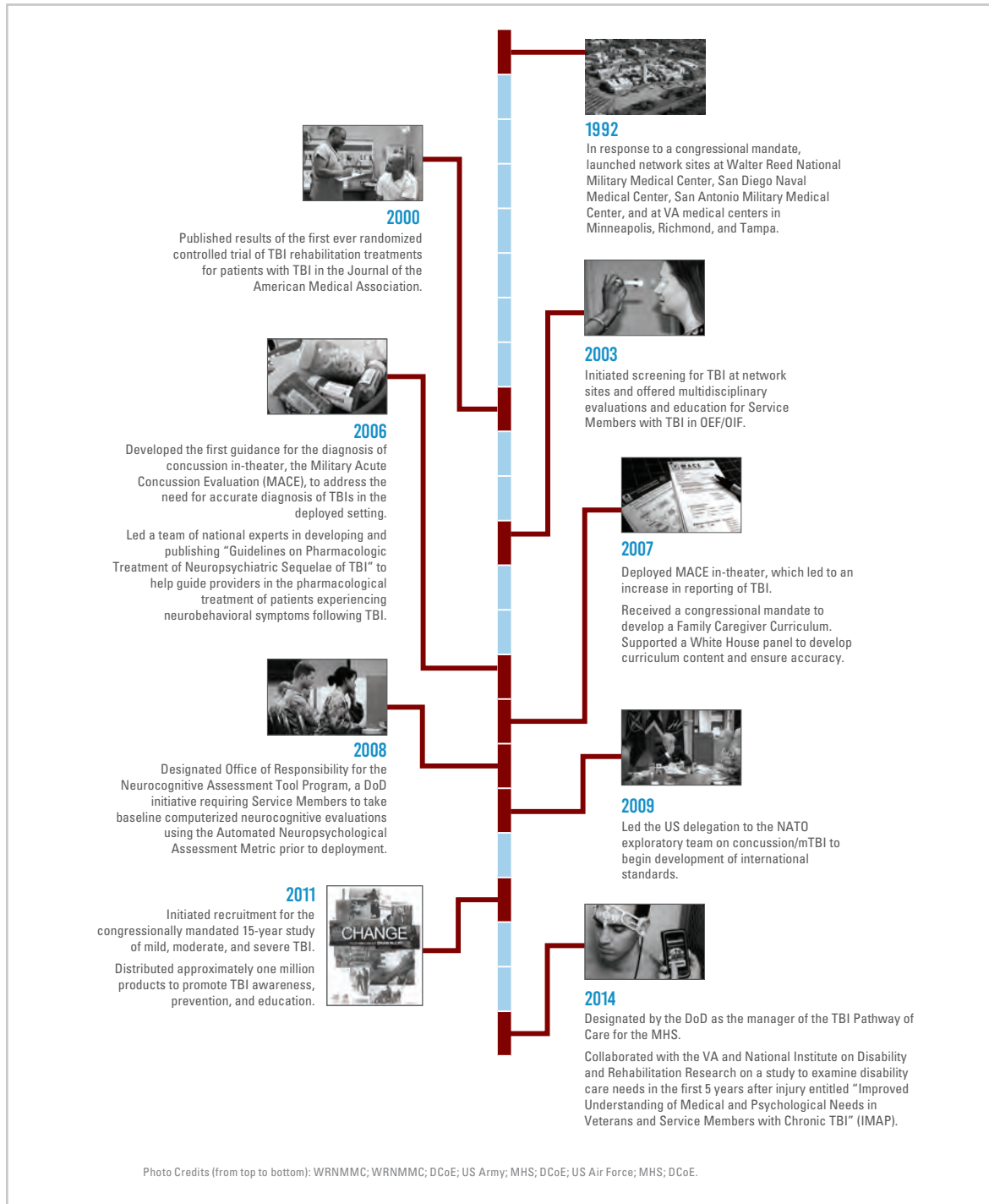
**TABLE 5-1: DCoE Centers**

DCoE Centers
<b>DVBIC</b> serves as the TBI operational component of DCoE, assisting the DoD and VA in the optimization of care for Service Members and Veterans who have sustained a TBI during or outside of deployment through research, clinical care, and education.
<b>Deployment Health Clinical Center (DHCC)</b> serves as the psychological health operational component of DCoE, conducting critical research, developing clinical support tools and evidence-based treatments, promoting the integration of behavioral health into primary care, and providing program monitoring and evaluation services.
<b>The National Center for Telehealth and Technology (T2)</b> develops technology-based behavioral health assessment, screening, reference, and treatment tools to minimize the short- and long-term adverse effects of TBI and mental health conditions associated with Military service. T2 is comprised of clinical psychologists, researchers, designers, and technical specialists.

policy, and in-theater experience. Army COL Geoffrey G. Grammer, DVVIC's national director as of April 2016, was the department chief of research at the NICoE, served for eight years as the chief of inpatient psychiatric

services at WRNMMC, and completed multiple deployments to Iraq and Afghanistan. Previous national directors, including Army COL Sidney R. Hinds, Air Force Col Michael Jaffee, and Army COL Jamie Grimes, served as

**FIGURE 5-2: DVVIC Achievements**



in-theatre clinicians, bringing their hands-on experience to DVBIC.

### **TBI Pathway of Care**

In 2014, the DoD named DVBIC manager of the TBI Pathway of Care and chair of the TBI Advisory Committee (TAC). As manager of the TBI Pathway of Care, DVBIC works with the Services and VA, as well as non-military, non-governmental collaborators to unify clinical care, enhance research and education, strengthen an outcomes-based care system, and improve standardization of care across Military and Veteran populations. As TAC chair, DVBIC expedites the review and execution of policies and programs that improve TBI care for Service Members and Veterans.

### **Network Sites**

In 1992, DVBIC launched six network sites and has since strategically expanded to locations with the greatest need for TBI care across Military and Veteran communities. In FY16, the opening of new sites at Fort Gordon and the San Antonio VA medical center bring DVBIC's network site total to 17 (Figure 5-3). Specific activities vary at each DVBIC network site and can include conducting clinical research, offering education in military and civilian settings, providing direct care to Service Members, analyzing TBI injury data, and helping Service Members, Veterans, and their Families locate services. Network sites fall into three groups, including large research/polytrauma centers (e.g., WRNMMRC), high volume/high rotation military sites (e.g., Camp Lejeune), and VA sites.

### **Research**

DVBIC's Research Division advances the scientific understanding of TBI along the continuum of care by conducting and supporting clinically focused research that produces evidence-based knowledge. This knowledge drives approaches to clinical

management and care that improve treatment and outcomes for Service Members and Veterans with TBI. Through innovative clinical research and extensive collaboration, DVBIC researchers help patients, caregivers, healthcare providers, and policymakers take action and make informed decisions based on the latest science.

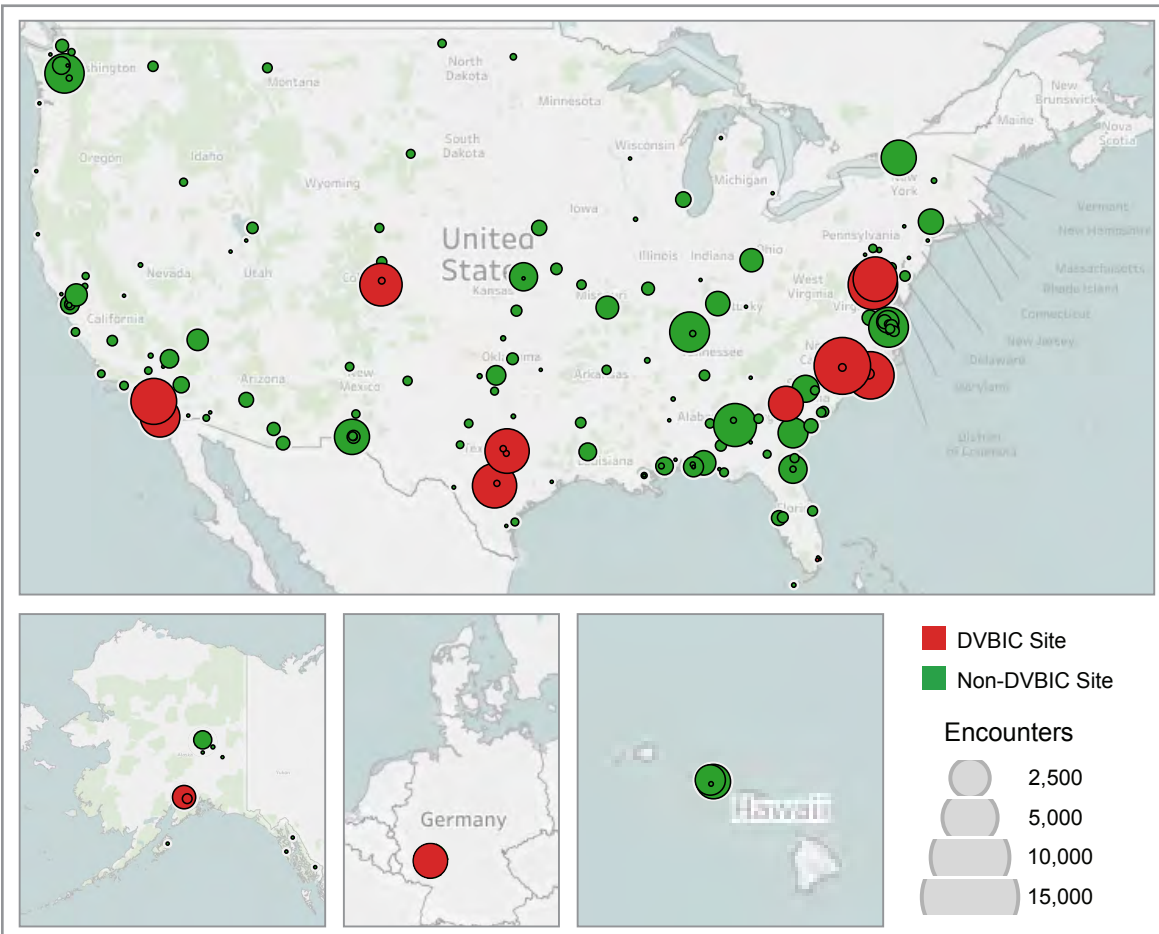
DVBIC researchers form the backbone of a clinically-focused DoD, VA, and civilian collaborative effort to advance the field of TBI care. DVBIC's extensive internal and external collaborations allow for clinical innovation and research, including prevention of injury, initial injury identification and management, medical evacuation, and acute and post-acute care and rehabilitation focused on returning individuals to their Family, community, and work or continued duty. The DVBIC research portfolio spans the continuum of TBI care and includes prevention, screening, diagnosis, treatment, rehabilitation and reintegration, as well as the natural history and long-term effects of TBI. Research Division objectives are fourfold:

- Investigate the efficacy of interventions for the prevention, diagnosis, and treatment of TBI.
- Conduct research across the entire range of TBI severities (e.g., mild, moderate, severe, and penetrating) in Service Members and Veteran populations.
- Develop and conduct epidemiological studies of TBI incidence and the unmet needs of TBI patients as well as their caregivers.
- Conduct imaging studies in order to determine the pathophysiological effects of TBI and the physiological basis of treatment interventions.
- Conduct and support congressionally mandated research studies.

A hallmark of DVBIC's approach to TBI is the link between research and clinical teams. DVBIC clinical researchers perform clinical duties relevant to their research, and clinicians at DVBIC sites often participate in data



**FIGURE 5-3: DVBIC Network Sites Mapped to TBI Encounters**



collection for research protocols.

### Clinical Affairs

DVBIC's Clinical Affairs Division supports state of the science TBI care by developing clinical recommendations for healthcare providers, analyzing outcomes, conducting TBI surveillance for the DoD, and providing subject matter expertise. The Clinical Affairs Division also assists Service Members and Veterans in accessing TBI clinical care, supportive services, and information throughout the continuum of care.

Through clinical suites developed by the Clinical Affairs Division, DVBIC optimizes TBI care by combining evidence from medical literature, healthcare research, and expert opinion to help providers deliver evidence-based treatment

and to address the challenges associated with TBI. Clinical suites include materials for both providers and patients, such as clinical recommendations, clinical support tools, training slides, and facts sheets. These materials provide guidance on the assessment and management mTBI symptoms, the evaluation and referral of mTBI patients for specialty care, and helping Service Members and Veterans cope with mTBI (Table 5-2).

DVBIC is also responsible for tracking worldwide TBI incidence for the US Military. Updated numbers are posted quarterly at <https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>. DVBIC's Clinical Affairs Division performs in-depth analyses on TBI-related data, including descriptions of risk and patterns of healthcare.

## Education

DVBIC's Education Division increases awareness of TBI across the care continuum by providing evidence-based knowledge through educational programs, activities, and resources ranging from prevention to recovery and reintegration. These efforts focus on educating and training providers, performing outreach to various stakeholder groups, and producing state of the science education and training resources.

DVBIC's Regional Education Program delivers TBI education and outreach in 14 regions around the US. Regional Education Coordinators (RECs) based at DVBIC sites serve as one of the most public

faces of DVBIC. RECs educate and train stakeholders, including Service Members, Veterans, Families, civilians, and providers, on TBI prevention, treatment, and recovery. REC emphasis varies depending on the needs of their site and in their catchment area.

## Collaboration and Partnerships

The cornerstone of DVBIC's success over the past 25 years has been collaboration. DVBIC maintains many successful partnerships based on deep relationships cultivated between DVBIC leadership and staff across the TBI community. These partnerships often result in collaborative

**TABLE 5-2: DVBIC Clinical Recommendations<sup>17</sup>**

Title	Year
Management of Headache Following Concussion/mTBI: Guidance for Primary Care Management in Deployed and Non-Deployed Settings	Feb 2016
Management of Sleep Disturbances Following Concussion/mTBI	Jun 2014
Progressive Return to Activity Following Acute Concussion/mTBI: Guidance for the Primary Care Manager in Deployed and Non-deployed Settings	Jan 2014
Progressive Return to Activity Following Acute Concussion/mTBI: Guidance for the Rehabilitation Provider in Deployed and Non-deployed Settings	Jan 2014
Neuroimaging Following Mild TBI in the Non-deployed Setting	Jul 2013
Assessment and Management of Visual Dysfunction Associated with mTBI (in collaboration with the Vision Center of Excellence)	Jan 2013
Assessment and Management of Dizziness Associated with mTBI	Sep 2012
Indications and Conditions for Neuroendocrine Dysfunction Associated with mTBI	Mar 2012
Indications and Conditions for In-theater Post-injury Neurocognitive Assessment Tool Testing	May 2011
Driving Following TBI	Jul 2009
Cognitive Rehabilitation	Apr 2009
MACE and Clinical Management Algorithms	Jun, Dec 2006; Sep 2012

opportunities essential to the success of DVBIC’s mission. For example, DVBIC network sites are collaborations between DVBIC, DoD MTFs, and VA medical centers. Partner cultivation, including the expansion to new network sites, remains a vital ongoing initiative.

Other partnerships involve organizations outside the network that are fully engaged and committed to the mission of DVBIC. These partners include the Centers for Disease Control and Prevention, NIH, and Washington Education and Television Association. Working with DVBIC, these partner organizations collaborate on current programs and initiatives, communicate at least quarterly, and have formal agreements in place with clearly defined desired outcomes. Some partners, such as Veteran Service Organizations and Military Support Organizations, share vested interests with DVBIC and obtain mutual benefits from their collaboration; however, they may not have formal agreements in place.

In May 2016, DVBIC evaluated its current partnership program and created an approach for program improvements. To maximize opportunities, DVBIC developed an inventory and partnership tracker, defined various partnership types, created preliminary goals, objectives, and measures for partnerships, and outlined an approach to guide future partnership activities.

### **DVBIC 2016 Contributions to Blast-related TBI**

DVBIC conducts and supports clinical studies that address blast-related TBI research needs recognized by the DoD, Congress, and the Executive Branch.

#### **NRAP-aligned Research**

In 2012, President Obama signed an Executive Order mandating the development of a NRAP directing the

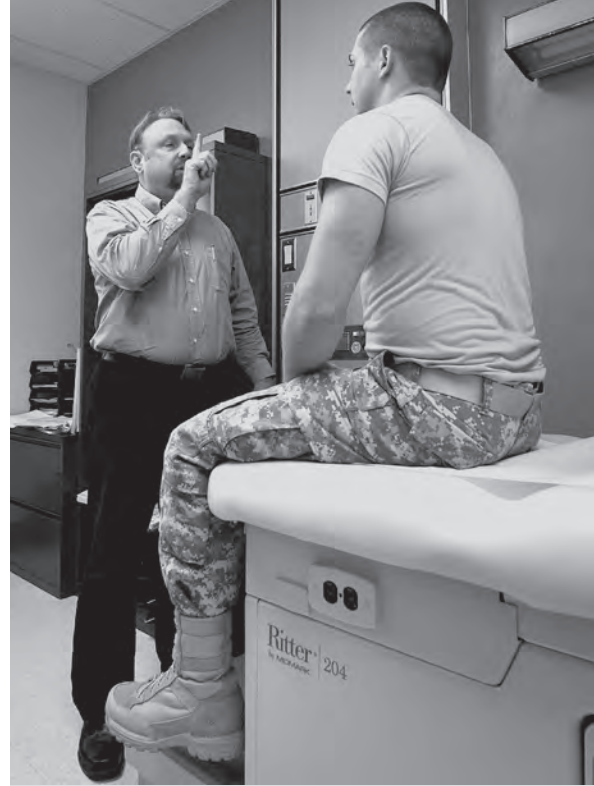


Photo credit: SSgt Christopher Hubenthal/US Air Force

DoD, VA, DHHS, and US Department of Education to coordinate efforts to advance PTSD and TBI research. The purpose of this plan was “to improve the coordination of agency research into these conditions and reduce the number of affected men and women through better prevention, diagnosis, and treatment.”<sup>18</sup> The NRAP designated key areas for research that align with active DVBIC protocols on blast-related and non-blast TBI (see Table 5-3).

### **DVBIC 2016 Active Protocols on Blast-related TBI**

The current DVBIC portfolio includes more than 60 studies, 38 of which are actively recruiting or pending institution review board (IRB) approval as of September 2016. All 38 active studies include patients with blast-related injuries. Three NRAP aligned DVBIC protocols enrolling patients in 2016 focus primarily on blast-related TBI:

**1. “Neurocognitive assessment of blast exposure sequela in training” (NC-BEST)** investigates the correlation among direct measures of blast exposure during combat training, subjective reporting of symptoms, and validated



**TABLE 5-3: DVBIC Research Studies that Align with NRAP Priorities**

NRAP Priority	DVBIC Study Examples
Foundational Science	<ul style="list-style-type: none"> <li>• Imaging support of study of cognitive rehabilitation effectiveness in mTBI</li> <li>• Retrospective analysis of brain morphometry in mTBI</li> <li>• Novel approaches to the analysis of clinic and Magnetic Resonance Imaging (MRI) data in Marines with a history of possible mTBI</li> </ul>
Epidemiology	<ul style="list-style-type: none"> <li>• Exploring the natural history of TBI within a military cohort-A longitudinal database and blood banking study: brief and comprehensive pathways (15-Year Study)</li> <li>• Deployment related mTBI: Incidence, natural history, and predictors of recovery in soldiers returning from OIF/OEF</li> <li>• Longitudinal, multi-domain assessment of neurodegeneration in Veterans</li> </ul>
Etiology	<ul style="list-style-type: none"> <li>• Investigating the neurologic effects of training associated blast</li> <li>• Neurocognitive assessment of blast exposure sequelae in training</li> </ul>
Prevention and Screening	<ul style="list-style-type: none"> <li>• A psychometric comparison of brief computerized neuropsychological assessment batteries: Validity and test-retest reliability</li> <li>• Assessments of the pupillary light reflex and eye movements for early identification of Service Members with acute mTBI</li> <li>• Structured telephonic testing 5 to 15 years after TBI</li> <li>• Discovery and validation of peripheral biomarkers of TBI</li> <li>• Retinal imaging with adaptive optics for early diagnosis of TBI</li> </ul>
Treatment	<ul style="list-style-type: none"> <li>• Study of cognitive rehabilitation effectiveness in mTBI (SCORE)</li> <li>• A randomized, double-blind, placebo-controlled study of the safety and efficacy of NNZ-2566 in the acute treatment of adults with mTBI</li> <li>• An outcome evaluation of alpha stimulation therapy on active duty Service Members with a history of concussion</li> <li>• A randomized controlled trial of interactive metronome technology for the remediation of cognitive difficulties following blast-related TBI</li> </ul>
Follow-up Care	<ul style="list-style-type: none"> <li>• Extending smart home technology for cognitively impaired Veterans to delay institutionalization</li> <li>• Long-term follow up of SCORE/iSCORE</li> <li>• Characterization and care coordination of polytrauma patients</li> <li>• Long-term outcomes from TBI</li> </ul>
Services Research	<ul style="list-style-type: none"> <li>• VA polytrauma rehabilitation center TBI Model Systems</li> <li>• A randomized controlled pilot study of the effectiveness and feasibility of novel rehabilitation approaches for patients with persistent complaints of cognitive dysfunction following TBI during OIF and OEF</li> <li>• Expanding our understanding of computer-based cognitive rehabilitation in the military population—a longitudinal brain fitness center database</li> </ul>

physiological and behavioral measures. NC-BEST addresses the NRAP priority of understanding the etiology of blast-related TBI by studying the impact of repetitive low level blasts as a cause of and risk factor for the development of TBI. NC-BEST also addresses the NRAP priority of foundational

science by exploring blast as an environmental factor causing TBI. DVBIC network site staff at Camp Pendleton and Naval Medical Center San Diego (NMCS) are conducting this research and presented two abstracts in August of 2016 at the Military Health System Research Symposium (MHSRS):



Photo credit: SSgt Evelyn Chavez/US Air Force

“Impact of Height on Service Member Blast Exposure Levels from Shoulder Mounted Rocket Launchers” and “The Impact of Lifetime Traumatic Brain Injury and Lifetime Blast Exposure History on Reported Neurobehavioral Symptoms of Service Members.”

**2. “Investigating the neurologic effects of training associated blast” (I-TAB)** examines the relationship between timing and intensity of blast exposures and the development of and recovery from physiological and behavioral changes. This study addresses the NRAP priority of etiology by increasing understanding of the impact of repetitive low level blast as a cause of and risk factor for the development of TBI. It also addresses the NRAP of foundational science by exploring blast as an environmental factor causing TBI. DVBIC staff at Camp Pendleton and NMCS D are conducting this research.

**3. “fMRI study of TBI associated with blast injury”** utilizes diffusion tensor imaging (DTI) and magnetization transfer imaging to investigate white matter integrity in relation to brain activation while subjects perform

cognitive tasks during functional magnetic resonance imaging (fMRI). Study participants are Veterans and Service Members who sustained a TBI in Iraq or Afghanistan. This research investigates brain regional volumes of gray matter and white matter on MRI in these military participants and studies potential comorbidities (combat and deployment-related stress, current emotional status, and depression). It addresses the NRAP priorities of treatment and follow-up care and is being conducted by DVBIC staff at the San Antonio Military Medical Center.

### DVBIC 2016 Publications on Blast-related TBI

Since 1992, DVBIC researchers have published more than 400 studies of TBI in peer-reviewed journals.<sup>19</sup> In the 2016 calendar year, DVBIC published 32 peer-reviewed journal articles, all of which include blast-related TBIs in the population being studied. Four of these articles specifically address blast related findings:

**1. “Laboratory impulsivity and depression in blast-exposed military personnel with post-concussion syndrome.”**<sup>20</sup>

Service Members with blast-related TBI may





experience a collection of symptoms known as post-concussive syndrome (PCS). Cognitive dysfunction is common in these patients, but they may also display increased impulsivity and impaired mood regulation. These factors may increase the risk of substance abuse and suicidal behavior. This research assessed the relationship between depressive symptoms and behavioral inhibition among 117 Service Members with blast-related TBI and a diagnosis of PCS. Researchers utilized a variety of tools: a modified version of the Rivermead Postconcussive Symptom Questionnaire (RPQ), the Center for Epidemiological Studies-Depression Scale (CES-D), the PTSD Checklist 5 (PCL-5), and the Continuous Performance Test II (CPT-II). The results are consistent with previous research demonstrating impaired mood regulation and behavioral inhibition in military TBI patients. TBI not only affects thinking but also mood and inhibition. This research may prove useful in identifying TBI patients with affective and inhibition problems.

## **2. “Headache in military service members with a history of mTBI: A cohort study of diagnosis and classification.”<sup>21</sup>**

Post-injury headache is a common symptom after mTBI. However, no instrument currently exists to categorize or track this symptom. In this study, researchers collected information on demographics, injuries, and headache characteristics for 95 patients seen between August 2008 and December 2009 at Womack Army Medical Center, Fort Bragg, North Carolina. Patients reported a total 166 headaches. The most common type of injury reported was blast (53.7 percent). The most frequently diagnosed headache type was continuous with migraine features (18.7 percent), then

chronic migraine (8.4 percent), migraine with aura (6 percent), hemicrania continua (7.2 percent), chronic cluster (3.6 percent), and non-classifiable (3 percent). The frequency of migraine headache among patients with concussion appears higher than expected, but this finding necessitates further research. Headache is a common symptom after concussion. However, less is known about its variation among TBI patients. This research impacts the Service Member by describing the frequency and type of headaches in a military TBI patient population.

## **3. “Distinction in EEG slow oscillations between chronic mTBI and PTSD.”<sup>22</sup>**

Resting state electroencephalogram (EEG) information differs between patients with mTBI and healthy controls. However, experts disagree on whether this change is stable. In addition, comorbid psychiatric conditions such as PTSD may contribute to long-term changes in EEG patterns. Recognizing the potential for comorbidity is particularly relevant in combat Veterans who often experience post-deployment stress. This research addresses the problem of comorbidity by measuring spectral power (type of EEG information) in a large sample of Service Members with blast exposure but varying degrees of TBI and PTSD severity. An increase in low frequency power in the prefrontal and right temporal areas correlated with blast-related TBI. However, a decrease in low frequency power in the right temporoparietal cortex correlated with PTSD. These results indicate that EEG may help to track neurophysiological effects and monitor recovery after TBI and differentiate pathophysiologies associated with TBI and PTSD. This research impacts the Service Member by identifying spectral patterns distinctive of TBI and PTSD.

#### **4. “Postconcussion symptoms reported by OEF/OIF veterans with and without blast exposure, mTBI, and PTSD.”<sup>23</sup>**

The 10th Edition of the International Statistical Classification of Diseases and Related Health Problems outlines criteria for PCS. This study addresses the validity of these criteria among Veterans of OEF and OIF by identifying relevant subscales from the British Columbia Postconcussion Symptom Inventory (BC-PSI) and examining group differences between Veterans with and without blast exposure, mTBI and PTSD. The sample included Veterans with blast-related mTBI (n = 47), blast exposure but no mTBI history (n = 20), and no blast exposure (n = 23). In total, 37 participants were diagnosed with PTSD, 53 were not. An exploratory factor analysis of BC-PSI followed by a multivariate analysis of variance to examine differences in subscale scores of the BC-PSI yielded by blast exposure, history of mTBI, and PTSD. BC-PSI factors were interpreted as cognitive, vestibular, affective, anger, and somatic factors. Vestibular, affective, and somatic factors were significantly higher for Veterans with blast exposure plus mTBI than for controls, but not significantly different for those with blast exposure but no mTBI. These results remained significant when PTSD symptom severity was included as a covariate. In addition, cognitive, anger, and somatic subscales were higher for Veterans with PTSD, though there was no interaction effect of PTSD and mTBI or blast history. The study demonstrates that the BC-PSI subscales can differentiate Veterans based on blast exposure, mTBI history, and PTSD. The BC-PSI inventory may prove useful in categorizing the symptoms experienced by Service Members with TBI.

#### **High-Profile Longitudinal Research**

In 2007, Congress mandated research to investigate “the effects of traumatic brain injury incurred by members of the Armed

Forces serving in OIF or OEF on the members who incur such an injury and their families.”<sup>24</sup> DVBIC is fulfilling this mandate through three major studies, all of which take into account the effects of blast-related TBI:

**1. “Exploring the Natural History of TBI within a Military Cohort: A 15-Year Longitudinal Database and Blood Banking Study”** examines long-term physical and mental health effects of TBI. Known as the Natural History Study, this research will include participants with blast-related TBI and will document the trajectory of recovery for up to 15 years in a sample of Service Members and Veterans by creating a repository that contains sensory motor, neuroimaging, neurocognitive, neurobehavioral, clinical interview, and blood banking data.

**2. “Improved Understanding of Medical and Psychological Needs in Veterans and Service Members with Chronic TBI”** explores the healthcare needs and service availability for TBI patients. Known as IMAP, this study will determine the incidence and association of chronic health conditions with rehabilitation outcomes in Veterans and Service Members with TBI. It will also determine environmental and contextual protective and risk factors, including blast exposure, impacting ongoing life care needs, as well as describe perceptions of healthcare needs the first two years post-injury.

**3. “Health Related Quality of Life in Caregivers of Service Members with Military-Related TBI”** investigates the effects of caring for a TBI patient on Family members and caregivers. The purpose of this research is to better understand the impact of TBI — particularly moderate and severe TBI — on Family members, friends, or significant others who are providing assistance to a Service Member or Veteran following a TBI. Participants will include those caring for



Photo credit: SrA Julianne Showalter/US Air Force

patients with blast-related TBI. Researchers will also develop a measure of health-related QOL for these caregivers utilizing recent advances in measurement development.

### Way Forward

An important research priority for DVBIC is to study central nervous system (CNS) injury, including CNS injury resulting from blast exposure. Existing research on the effects of blast on biological tissue documents how exposure impacts particular organs such as the lung. However, significant knowledge gaps exist for blast-related CNS injury, including uncertainties about the mechanism of CNS injury following a detonation and blast wave.<sup>25,26</sup> Along with research on the mechanism of injury, DVBIC is also conducting and supporting research on recovery from blast-related TBI that will generate evidence-based knowledge on long-term neurocognitive and pathophysiological consequences and outcomes.

The prevalence of TBI in military and Veteran populations, both as a result of blast and non-blast injuries, underscores the need for continued advancement in the scientific understanding of issues surrounding TBI. With its 25-year legacy as a TBI thought leader, DVBIC is uniquely positioned to address the uncertainties related to TBI care, education, and research. While recent world events have created an unknown future, DVBIC is responding to the TBI mission through the identification, evaluation, and dissemination of best practices for the evaluation and treatment of blast-related TBI. As the TBI Pathway of Care manager, DVBIC partners with Service and VA TBI program leads to create a positive future for those who sustain TBIs centered on the optimization of patient outcomes through development of objective measures of blast-related neurotrauma and identification of factors that enhance recovery.



06



CHAPTER 6:

# WARRIOR INJURY ASSESSMENT MANIKIN

## Dedication

This chapter is dedicated to the HON Dr. J. Michael Gilmore who served as the Director of Operational Test and Evaluation (DOT&E), OSD from 23 September 2009 to 20 January 2017. Dr. Gilmore’s technical rigor and pledge to provide meaningful and credible test results to the Congress and civilian and military leaders led to the creation of the WIAMan S&T project. It is also dedicated to Dr. Terry Rauch, the Director of the Defense Medical Research and Development Program (DMRDP) within the DHA, and Ms. Mary Miller, the Acting ASD(R&E) and the former Deputy Assistant Secretary of the Army for Research and Technology. They too deserve special recognition for their leadership and guidance and for prioritizing the WIAMan S&T project. Finally, this chapter is dedicated to all who have donated their bodies to science. Without these acts of generosity, the execution of the WIAMan project – needed to protect America’s Service Members from threat effects encountered in combat—would be impossible. These donors and their families are true heroes.



**O**n 15 September 1916, on the battlefield at Flers-Courcelette France, the British Army introduced a new weapon, the tank, and an enduring battle between lethality and protection ensued. One of the first countermeasures to the tank was landmines, which used explosive blast or blast-driven projectiles to damage the vehicle and injure or incapacitate the crew. Because the tank caught the enemy by surprise, the first landmines were hastily created from explosive devices at hand, artillery shells and mortar projectiles, and what could be improvised, such as wooden boxes filled with explosives and fitted with a trigger mechanism. After more than 100 years of military progress, all types of ground vehicles operating “outside the wire” remain at risk to this threat, which is often still deployed in crude and improvised devices. Recent experience during OEF and OIF has shown that vehicles and their occupants remain vulnerable to the effects of mines or IEDs which

detonate on or below the surface of the earth as the vehicle passes over them. An attack of this type is referred to as under-body blast (UBB). Severe UBB threats can propel massive vehicles several feet into the air while simultaneously ripping off external components and deforming or damaging the crew compartment (Figure 6-1). Occupants suffer the effects of severe upward acceleration and the slam-down as their vehicle falls back to earth. And if the vehicle was moving at the time of the attack, the occupants may face additional consequences

**FIGURE 6-1: Under-body Blast Test**



Photo credit: RDECOM

Photo credit (opposite page): RDECOM

*The new Army WIAMan technology demonstrator, on the right, the world’s first crash-test dummy designed for the use in the military under-body blast environment, displays its enhanced human-like response as compared to the Hybrid III automotive crash-test dummy, left, that is currently used for predicting injury risk.*





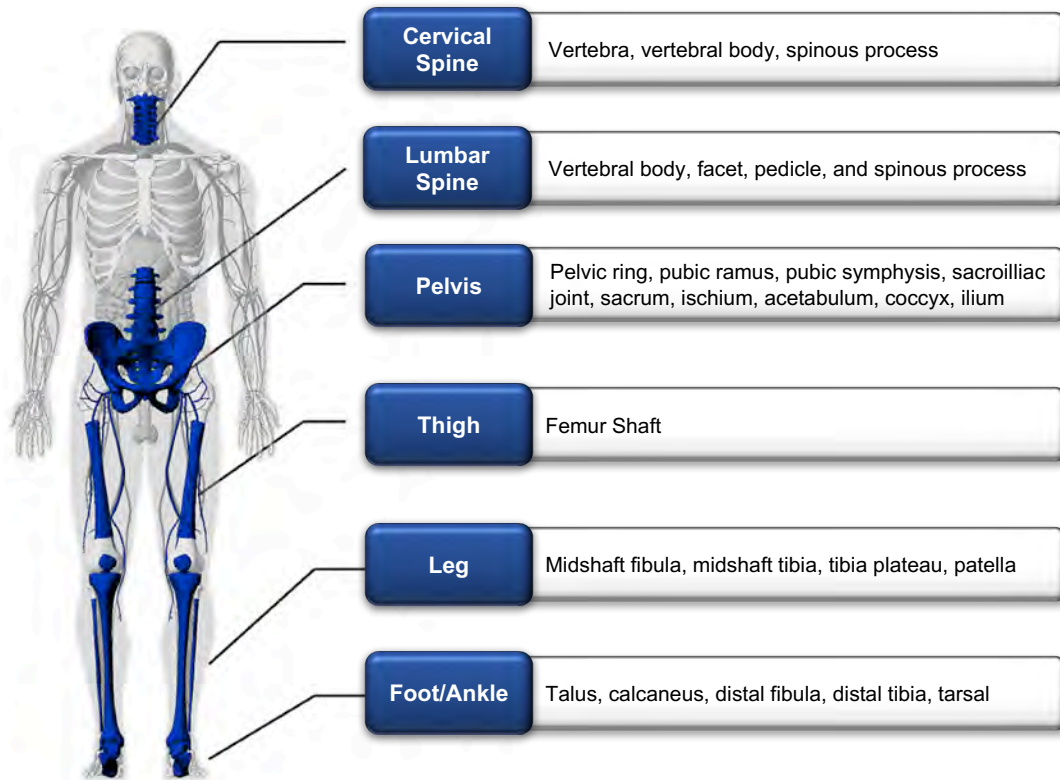
Photo credit: RDECOM

from subsequent collisions or even roll-over of the vehicle. Research has characterized the physics of UBB which has led to advances in protection technologies and vehicle designs that greatly reduce the risk of catastrophic failure and its overwhelming consequences. However, even if the crew compartment of the vehicle remains intact, occupants are still subjected to severe local and global accelerative loading. To be clear, the injury causing mechanism of concern is the coupling of the blast products (overpressure and accelerated soil, rocks, and debris) to the vehicle structure which transmits them in turn as an accelerative load to the vehicle occupants, primarily in the vertical direction. These loads are transmitted into the occupants at the points where they are in contact with the vehicle; feet on the floor and upper legs-pelvis-torso in the seat. When exposed to this loading, occupants suffer injuries which can be so severe that they can't complete their mission and can't egress from the damaged vehicle. They can be so severe that Service Members suffer life-changing medical complications, and sometimes, they make the ultimate sacrifice. Data on injuries sustained by mounted Service Members due to UBB attacks are compiled by the Project Office for JTAPIC at USAMRMC. For UBB attacks that are not catastrophic, the primary injuries observed are skeletal, ranging from simple fractures to

traumatic amputations. The distribution of observed skeletal fractures are shown in Figure 6-2. The PCO at the USAMRMC executes a program through which they determine the blast injury priorities of the Medical and Materiel communities using a process referred to as the BIPSR Process. Based on the priorities of this COI, the BIPSR Process engages SMEs to review all existing research and data with the goal of identifying relevant prevention standards for the blast injuries of concern. Through the BIPSR Process, the PCO has confirmed that skeletal injuries caused by UBB are a high priority concern for both the Medical and Materiel communities. Through an SME review, the BIPSR program has determined that there is insufficient information available on the human response and vulnerabilities to accelerative blast loading injuries and thus it is not possible to recommend protection standards for this priority area. This finding confirmed that a critical knowledge gap exists for RDT&E and acquisition of protection and vehicle technologies and within the domain of MOM. Sun Tzu, the well-known Chinese General of the sixth century, is quoted as saying "If you know the enemy and you know yourself you need not fear the results of a hundred battles." In the quest to prevent the skeletal injuries caused by the severe accelerative loading associated with UBB, the DHP and the US Army Research



**FIGURE 6-2: Domains of Interest for Skeletal Injuries Caused by UBB**



and Technology activity are heeding this admonition to “know yourself.” Together, they have resourced the WIAMan S&T project. Using a multi-disciplinary approach merging ballistic science, injury biomechanics, medical forensics, and other science and engineering disciplines, the WIAMan S&T project is creating the knowledge-base on how mounted Service Members respond to and suffer skeletal injuries in the extreme conditions caused by UBB. To protect the mounted Service Members of tomorrow, that knowledge is being used to create a new test and analysis capability that can determine the risk of such injuries. This capability will be in a form that is usable throughout the RDT&E enterprise. It will be equally suitable for informing acquisition decision and for guiding the development of protection technologies. Simultaneously, the WIAMan S&T project is creating the critical data needed to develop and validate the next generation capabilities for predicting injury risk in this environment; namely modeling and analyzing the effects of severe environments

on Service Members through physics-based modeling and simulation of the actual human body in all its anatomical complexity.

### **Goal: Service Members Protection through Scientifically Valid Injury Risk Criteria and Test and Analysis Tools and Methods**

Many types of military equipment are fielded to protect Service Members from the myriad of threats faced in combat. Some equipment protects by preventing threats from ever reaching the Service Members while others, such as helmets and body armor, provide protection when they do. Technologists and analysts leverage all manner of research and empirical data in order to create criteria which can be used to judge if the equipment can protect the Service Members as required by military necessities. These criteria, combined with knowledge of the hazardous environment, are used to conceive tools, techniques, instrumentation, and metrics with the goal of objectively testing materiel solutions to

determine if they meet protection requirements. The test outcomes must provide the means to evaluate vulnerability of Service Members in a manner that is consistent, objective, and scientifically valid. Within the US Army, the Army Test and Evaluation Command (ATEC) conducts such tests and the Survivability/Lethality Analysis Directorate (SLAD) of ARL analyzes the test results to assess the risk of human injury. To achieve the goal of protecting mounted Service Members from the UBB threat, physical testing of vehicles and their protective equipment is essential and well established Test Operating Procedures are in practice. Explosive devices are detonated underneath partial or complete vehicle structures while various instruments monitor their response to the blast. Of primary interest is the structural integrity of the crew compartment, however, for the reasons stated previously, it is not enough to test just this attribute. A means is needed to assess the injury risk faced by the vehicle occupants even if the crew compartment survives; like eggs in a carton, the humans within are more vulnerable than the structure. In 1972, the US Army explored the use of an instrumented Anthropomorphic Test Device (ATD), a.k.a. crash-test dummy, in vehicle UBB testing as a means to evaluate the risk of skeletal injuries when mounted Service Members are subjected to the effects of UBB. Leveraging work performed by the civilian automotive safety community, the US Army experimented with an ATD which is known today as the Hybrid III. This ATD was developed to assess the risk of skeletal injury for the civilian driving population under frontal car crash conditions. This early version of the Hybrid III demonstrated sufficient ruggedness and usability in the UBB environment and it was adopted for blast testing of vehicles. It remains in use today by the RDT&E enterprise of the US Army, and by many allied nations. The Hybrid III is routinely used in laboratory testing for such activities as understanding the physics of UBB loading and to assess the protection offered by new vehicle seat

technologies. It is also used in congressionally mandated Live Fire Test and Evaluation, so called Title 10 LFT&E, as described in 10 US Code §139, which is performed to evaluate vehicle survivability under realistic conditions. The outcomes of Title 10 LFT&E are essential to achieving approval to initiate procurement of weapon systems. In 2010, after conducting an intensive program to rapidly develop and deploy the Mine Resistant Ambush Protected (MRAP) family of vehicles, the limitations of DoD capabilities for solving challenges associated with protecting Service Members from the effects of UBB became clear. A capability gap study conducted by the US Army at the direction of then SECDEF, the HON Robert M. Gates, defined important shortcomings associated with capabilities for modeling and testing the effects of UBB. One of the conclusions of this study was that the Hybrid III ATD was inadequate for assessing the risk of skeletal injuries in UBB testing. In reaching this conclusion, standards created by the US Department of Transportation (DOT) for scientifically valid, ATD-based injury assessment, were given significant weight. For automotive safety testing, the DOT has developed a four-part objective standard that must be met before an ATD is incorporated into regulated use as defined in Part 572 of Section 49 of the Code of Federal Regulations. While the Hybrid III ATD meets that standard for frontal car crash testing, it does not meet that standard for UBB testing in the military environment. Deviations from the DOT standard include:

1. lack of evidence that the ATD is repeatable and reproducible under UBB loading conditions
2. durability issues that can affect sensor measurements
3. anthropometry limitations including the ability to achieve the correct posture and to accommodate the PPE worn by Service Members
4. lack of knowledge of the degree to which the Hybrid III exhibits the appropriate

human-like response to UBB loading conditions (an attribute of an ATD known as biofidelity)

5. lack of criteria for assessing the risk of observed injuries

Some of these deviations derive from the fact that the Hybrid III was designed for use in frontal car crash safety testing, in which the applied loads are in the horizontal plane and from the front, while in a UBB test, the applied loads are in a vertical plane and from below. In addition, the automobile crash conditions for which the Hybrid III was designed occur at a lower loading rate and with less severity than those caused by UBB. Other deviations result from the fact that the use of the Hybrid III was not enabled by an appropriate investigation of human injury biomechanics under UBB loading conditions. This deviation is the most critical because only through such investigations is it possible to characterize the response of humans to a hazard like UBB. Investigations of this type require testing with human cadavers or, as they are sometimes referred, postmortem human surrogates (PMHS). Conducting tests with PMHS is essential for developing and validating an ATD-based injury assessment capability. However, such work is complex, resource intensive and, for ethical reasons, undertaken only when a clear need is identified. Lacking the required data, the DoD found it necessary to apply injury criteria derived from a variety of prior biomechanics research, little of which was representative of military UBB conditions.

In addition, since Title 10 LFT&E includes both testing for compliance with requirements and a consideration of overmatching threats, the available injury criteria, which were developed primarily for automotive safety compliance testing, lacked the necessary robustness and statistical power.

Using a crash test dummy in a hazardous environment that it was not designed for and without the benefit of appropriate injury biomechanics knowledge has significant risk. In fact, the DOT has recognized that ATDs, or

crash-test dummies, must be designed to reflect the population to be protected, compatible with the hazardous environment in which they will be used, and capable of predicting the injuries that occur within this hazardous environment. As a result, in addition to frontal crash dummies, the DOT has developed and put into regulated use ATDs that are purpose-built for many different crash scenarios. For example, in automotive safety testing there are unique ATDs for assessing injury risk for front, side, and rear impact as well as ATDs that represent adults of different physical size, pregnant females, and children.

As the proponent for Title 10 LFT&E, the HON Dr. J. Michael Gilmore, determined to resolve the shortcomings in the ability to predict the risk of skeletal injury risk for mounted Service Members exposed to UBB. Through his initiative, in 2011 an ambitious S&T project was initiated to demonstrate the feasibility of creating the first purpose-built ATD for the military UBB environment. Today, the WIAMan Engineering Office (WEO) at the ARL is leading this S&T effort to develop and demonstrate an instrumented ATD for the military UBB environment. The goal is to meet the injury risk assessment requirements of the DoD and to enable a prompt introduction of this new test capability to benefit Service Members. The WIAMan S&T project is unique as it comprises a fully integrated effort to:

1. understand the nature of skeletal injuries observed in recent combat events
2. conduct the largest ever DoD skeletal injury biomechanics effort to create the data and knowledge products needed to design and implement a purpose-built UBB ATD
3. fabricate, evaluate, and refine Technology Demonstrator (TD) ATDs
4. conduct other activities needed to implement a purpose-built ATD for the military UBB environment

In 2015, the WEO established a partner to assist in transitioning S&T solutions into practice in



Title 10 LFT&E, the Program Executive Office for Simulation, Training, and Instrumentation (PEO-STRI). As the WEO completes this unique S&T effort to demonstrate the feasibility of the first-ever ATD to be purpose-built for the military UBB environment, PEO-STRI is laying the groundwork for accepting the products from the S&T effort and for establishing a program to acquire and deliver this new capability to ATEC and SLAD.

### Oversight and Execution of WIAMan

Within OSD, the Director of DOT&E provides oversight of the services and execution of Title 10 LFT&E. Because a valid ATD is needed to assess the survivability of mounted Service Members when conducting Title 10 LFT&E, the DOT&E sponsored the effort to develop and demonstrate a new ATD-based injury assessment capability for UBB testing. The DOT&E provided overarching guidance on the capabilities required for WIAMan.

That guidance was based on the deficiencies and capability gaps identified through the Gates

study and through DOT&E's experience with the MRAP vehicle program. The WIAMan S&T program was formally established in 2011 through a Resource Management Decision which also established a Senior Steering Group (SSG) to provide oversight. The SSG is co-led by DOT&E and a representative from the Office of the Under-Secretary of Defense for Acquisition Technology, and Logistics (USD (AT&L)). The members of the SSG include a representative from the ASD(HA), the Deputy Assistant Secretary of the US Army for Research and Technology (DASA R&T), the Commanding General of the US Army Research Development and Engineering Command (RDECOM), the Commanding General of the USAMRMC, the Director of the ARL, the Commanding General of the ATEC, and the PEO-STRI. The WIAMan S&T project is led by the WEO of the ARL, an element of RDECOM. The Tank and Automotive Research Development and Engineering Center (TARDEC), another element of RDECOM, is also a member of the WEO team. The WIAMan S&T effort is funded by DASA R&T and the

**FIGURE 6-3: Organizations Playing a Role in WIAMan**



ASD(HA). Upon demonstration by the S&T effort of a feasible purpose-built UBB ATD, it is the goal of the DOT&E to see that the current ATD, the Hybrid III, is replaced by this new capability. The manner in which this will be achieved is still under discussion. However, an important step toward meeting this goal has been the creation of a Test Capability Requirements Document (TCRD) by ATEC and RDECOM. The TCRD reflects the overarching guidance from DOT&E and enumerates testable and measurable threshold and objective requirements which are guiding the S&T project and which will ultimately be used to evaluate and judge the ATDs that replace the Hybrid III. To execute the unprecedented WIAMan S&T project, the WEO has assembled a team comprised of other government agencies, academia, and industry, both national and international. Those organizations are shown in Figure 6-3.

### Scope of the WIAMan Project

The JTAPIC Program Office has compiled the list of injuries suffered by mounted Service Members during OEF and OIF as a result of UBB attack, and it is disturbingly extensive. It includes skeletal, visceral, neurological, and other injuries. This data was the starting point for defining the scope of the WIAMan S&T project. Additional scoping decisions were made to assure that the S&T project stayed focused on the overarching guidance provided by the DOT&E and that it produced a feasible technical solution that can be implemented in the Title 10 LFT&E environment, as well as in the RDT&E environment. Through coordination and review with the WIAMan SSG members, agreements were reached on the scope of the Army S&T effort. It was agreed that the S&T project will produce and demonstrate a fully functional TD ATD that is purpose built for use in the military UBB environment. The TD will represent a 50th percentile, male anthropometry based on the current US Army Service Members population. The ATD will be designed for use

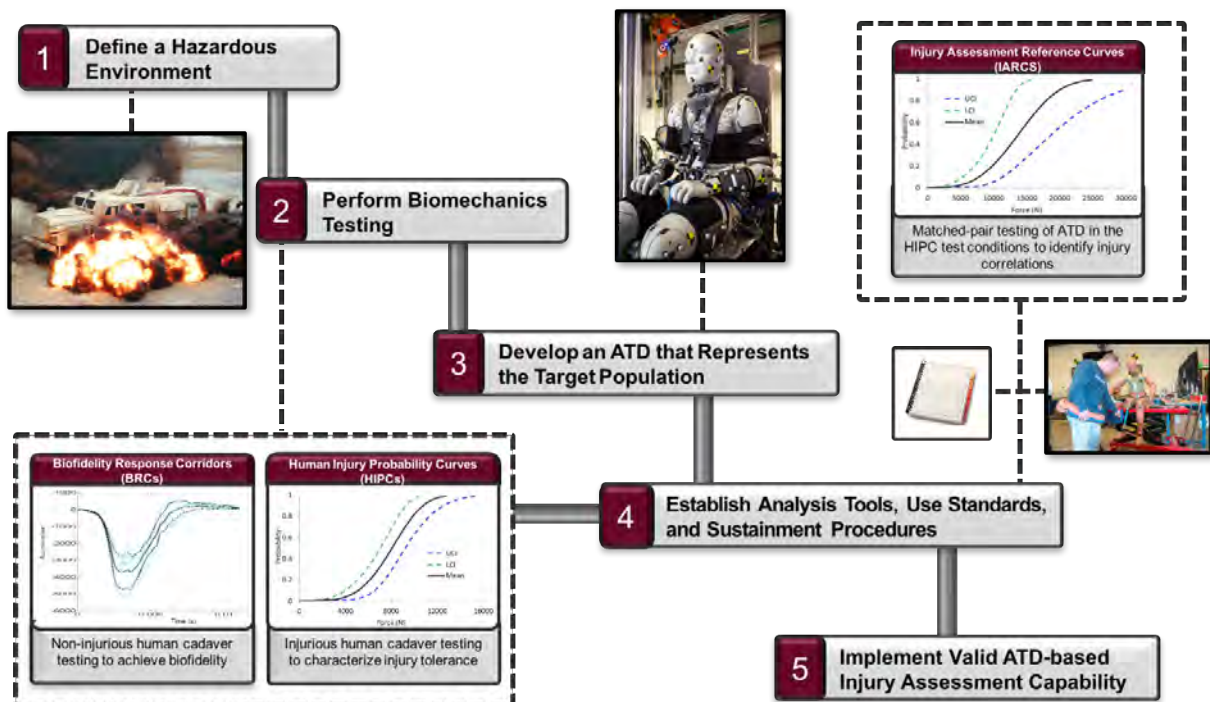
in a seated posture and only for skeletal injury risk assessment for the UBB vertical accelerative environment, e.g., not automotive frontal or side crash, or roll-over conditions. Other natures of blast-induced injury; BOP, projectile penetration, blunt impact, burns or other thermal induced injuries will not be considered, and neither will blast-related chemical or biological injuries. In addition, there will be no effort to develop ATDs of other sizes, e.g., an ATD with 5th or 95th percentile anthropometry, as exist in the automotive safety community. The S&T project will address skeletal fractures of varying severity, consistent with theater injury data. The biomechanics task will not investigate human response or injuries in standing or prone postures. Because the WIAMan biomechanics task is based on testing PMHS, there is no ability to assess neurological injuries whose diagnosis requires that the subject be alive. As a result, the study of TBI was deemed to be out-of-scope. It was also determined that visceral or organ injuries will only be considered if they occur in conjunction with the tests conducted to investigate skeletal fracture. If such a co-morbidity is consistently observed, and if the injury outcome can be correlated to sensor data used for assessing skeletal injury risk, then an attempt will be made to incorporate it as part of the new capability. Finally, while there will be no effort made to develop a female ATD, an exploratory biomechanics investigation will be performed with the goal of determining whether or not there are significant differences in the risk of skeletal injury based on the anatomical differences between males and females. It was also agreed that the effort will create and use a validated finite element analysis (FEA) model to define and enhance the design of the ATD. The FEA model will transition to SLAD for use in pre-shot predictions for Title 10 LFT&E and developmental testing and for promulgation to others in the RDT&E community who have a need to assess UBB injury risk in virtual experiments.

## Approach

Most people are familiar with ATDs by seeing images of them in advertisements by automobile manufacturers touting the safety of their vehicles. Viewed in that way, the simple human-like form of an instrumented ATD belies its technical sophistication. An ATD can be thought of as the integration of two physical subsystems. One, is the manikin, or human-like structure, and the second is the instrumentation, sensors and data recorders that are installed within the manikin or used in conjunction with it. The manikin structure must have sufficient anthropometric detail to represent the target population and interact appropriately with the environment in which it will be used. It must also be robust enough to withstand the extreme loads of the hazardous environment without failing while simultaneously responding in a human-like manner. Care must be taken in the design to include sufficient anatomical resolution such that it can predict relevant injuries.

The manikin structure must be capable of integrating the sensors which will measure physical quantities, such as force or moment, at a location within the manikin that demonstrates a strong correlation to the skeletal injuries whose risk must be predicted. Likewise, the data recording devices must have sufficient resolution to enable evaluation of the injury criteria. These requirements lead to designs that have much in common with the human skeletal structure, albeit in a simplified fashion, and with features needed to achieve the correct response despite the extensive use of metallic parts in them. To perform an injury risk test, an ATD is placed in the hazardous environment in accordance with well-established standards, where it is subjected to potentially injurious loading conditions. During the test, output signals from the sensors embedded in the ATD structure are captured on the recorders. Subsequent to the test, the data are processed and used in conjunction with biomechanics knowledge to assess the risk of a fracture in a

**FIGURE 6-4: Five-step Process for Developing, Demonstrating, and Implementing the Products of the WIAMan S&T Project**





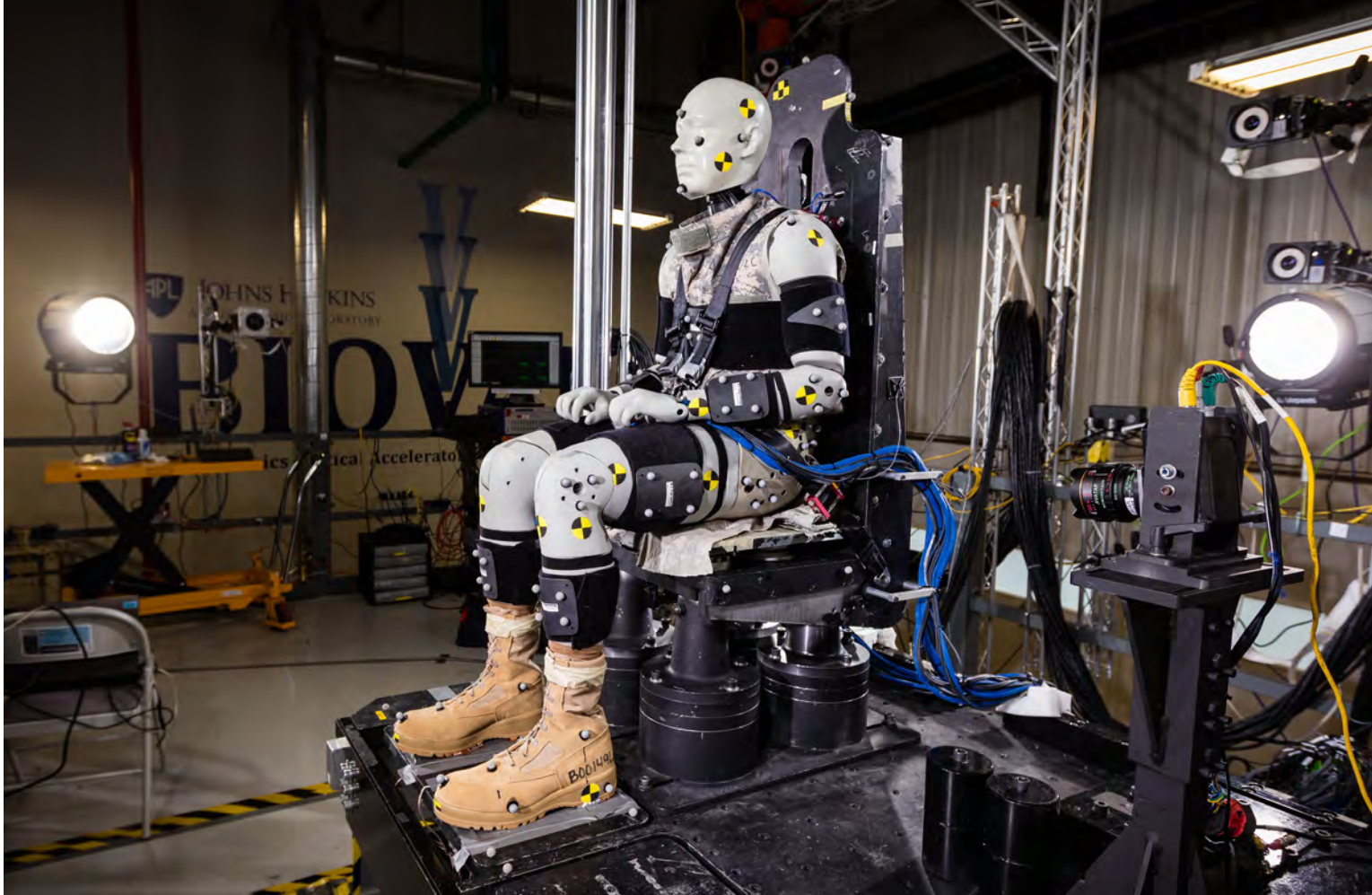


Photo credit: RDECOM and the JHU/APL

particular bone or body region. The biomechanics knowledge includes data on observed injuries, biomechanics test data, and relationships called Injury Assessment Reference Curves (IARCs) that correlate measurements made with the ATD to risk functions known as Human Injury Probability Curves (HIPCs) which describe the risk of a skeletal injury in terms of physical quantities such as force, acceleration, or moment.

As shown in Figure 6-4, the first step in creating an ATD-based injury assessment capability is a detailed understanding of the hazardous environment. This includes understanding the population experiencing the hazard, the manner in which they work and operate within the environment, and the injuries that the population is known to be at risk for; in the case of WIAMan, skeletal injuries. To create an ATD for UBB, the WEO performed detailed analysis on the loading environment experienced by seated, mounted Service Members using data measured in vehicle UBB tests and insights from physics-based simulations and analysis. In addition, as discussed previously, the

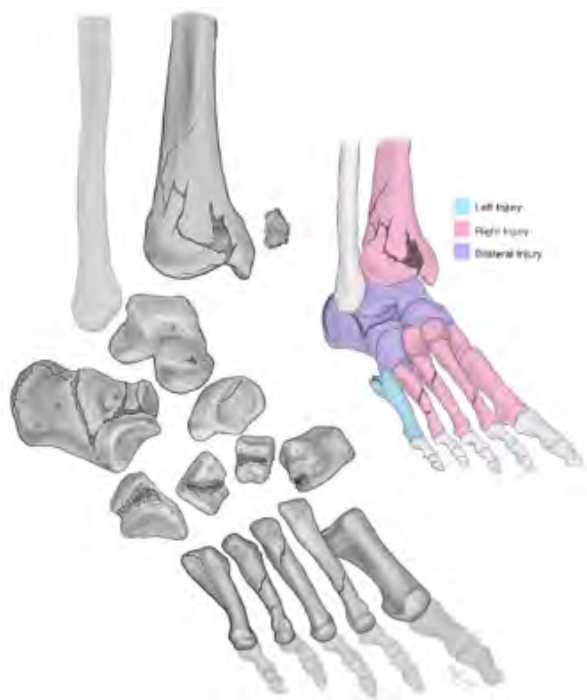
WEO leveraged the JTAPIC program for data on injuries experienced by Service Members in OEF and OIF, including, for the first time, a detailed analysis of de-identified clinical images of skeletal injuries suffered by Service Members. These images provided essential information about the morphology of the skeletal fractures which revealed information about the loading conditions within the human body that were responsible for the injury. The description of the environment was completed by considering such things as posture, leg position, restraint systems, as well as the clothing and PPE worn by mounted Service Members such as body-armor and footwear. A recent study of current soldier anthropometry, performed by RDECOM, was leveraged to provide the data needed to define a 50th percentile Service Members, the target anthropometry for the WIAMan ATD.

With the environment defined, the WEO tackled step two of the process, and the most challenging aspect of creating this new capability; establishing and executing an injury biomechanics task to produce the data needed to drive the

design of the ATD and to produce the HIPC, the foundation for a scientifically valid injury assessment capability. Biomechanics tests of this nature are inherently hazardous to humans, thus they are performed using cadavers or PMHS. The practice of conducting hazardous tests with anatomical gifts has been used for decades to enhance transportation safety. The Army leveraged this prior experience, which exists primarily in academia, to establish an injury biomechanics team with the appropriate expertise, capabilities, and capacity to meet the aggressive goals of the project. Led by the JHU/APL, the team also includes academicians, principal investigators, and researchers from the Medical College of Wisconsin, the University of Michigan Transportation Research Institute, the Wayne State University (WSU), The Ohio State University (OSU), University of Virginia (UVA), Virginia Polytechnic Institute and State University (VT), Duke University, and the Wake Forest University (WFU). The WEO biomechanics task includes sub-injurious tests to establish design guidelines for the ATD in the form of Biofidelity Response Corridors (BRC). The other type of biomechanics testing is performed to produce injury risk data. It is from this data that HIPCs will be created. The final knowledge product that will be produced by the WIAMan S&T project team will be the IARCs, which provide the correlation between the injury risk measured in the cadavers and the measurements obtained from the sensors mounted in the ATD. Development of the ATD, the third step in the process, is being performed through contracts with industry specialists. Although the current Hybrid III ATD was found to be inadequate, the many years that it was used for UBB testing provided knowledge that guided the development of the new capability as did recent efforts to upgrade ATD technology for automotive safety compliance testing. Every effort was made to leverage the experience of developing newer automotive ATDs, in particular the WORLD-SID, side impact ATD, developed by the International

Organisation for Standardisation (ISO), and the THOR, an advanced front crash ATD developed by the National Highway Traffic Safety Administration, and their technologies. In step four the related products are developed to ensure the ATD is used in an objective and valid fashion and that it can be sustained by ATEC. Like any precision instrument, an ATD must be maintained and operated in accordance with standards that assure consistency, reproducibility, and accuracy. This also includes the management and analysis of data that is captured by the ATD during a test. One of the most important elements of this is the establishment of test procedures that demonstrate that an ATD is functioning in accordance with biomechanical and instrumentation standards. This is achieved through a certification testing protocol which each ATD is subjected to prior to use in a test event. In addition, schedules and procedures for preventive and corrective maintenance and calibration must be established for use by ATD operators. Since these factors must be addressed during the S&T project, the WEO will also create this capability. Finally, in step five, the capability must be implemented within the LFT&E community. From an operations perspective, this will include procuring production ATDs, establishing logistics support including certification test equipment and other needed infrastructure and outlining a spare parts strategy. To support the use of the WIAMan capability by the analysis community, data libraries will be prepared as well as the algorithms and methodologies needed to perform objective analysis of WIAMan ATD data in order to produce injury risk assessments. In addition, per ATEC Regulation 73-21, all test instrumentation that is used to evaluate major defense acquisition programs (e.g., Acquisition Category 1) must undergo a formal Verification, Validation, and Accreditation procedure. The knowledge products and tools that are being compiled by the WEO will be essential to achieving accreditation of the new WIAMan

**FIGURE 6-5: Skeletal Injuries Observed in WIAMan Biomechanics Testing** (Anatomical drawing courtesy of Ms. Autumn Kulaga-Souza, ARL)



capability. Of equal importance is the advanced coordination with vehicle acquisition programs that have a UBB survivability requirement. Replacement of the Hybrid III by the WIAMan capability means that these programs will be measured by a new “yard-stick” that is more accurate and which has higher resolution. While the introduction of WIAMan provides these programs with the opportunity to field vehicles with unprecedented safety, it must also be achieved without putting at risk the delivery of these improved vehicles to Service Members.

### **“Know Yourself:” Understanding Service Members Biomechanics in the UBB Environment**

It seems obvious that if one desires to prevent humans from being injured then one must study the nature of the insult or injury mechanism and how the human body responds to it. Of course, for ethical reasons, we don’t purposefully subject our fellow man to such treatment. Much knowledge can be derived from the practice of MOM; however the emphasis is more on treatment

than on obtaining a detailed understanding of the causes for the injury.

To obtain the necessary knowledge, the WIAMan biomechanics task exposes instrumented PMHS to UBB loading conditions to obtain actionable information about the vulnerability of humans to this severe environment. The first priority of this effort has been to develop the understanding of how a seated warfighter responds to the vertical accelerative loading caused by UBB at severity levels below those which cause injury. Conducting non-injurious tests of PMHS under these conditions, the WIAMan biomechanics task has produced the BRCs which describe the characteristics of human response to UBB loading. BRCs were given first priority because they are needed to guide the design of the structure of the ATD. The WEO has developed BRCs for the whole-body as well as for four specific body regions, head and neck, lumbar spine, pelvis, and the lower extremities. These four body regions were selected because of the injury data obtained through the JTAPIC program. As of the end of FY16, tests for these four body regions are complete and over 800 BRCs have been created. This includes 55 unique test configurations, multiple postures, and a wide variety of loading condition severity. In addition, more than 500 BRCs have been created from tests of whole-body PMHS. The whole-body testing will be completed by the end of the first quarter of FY17. As the BRC testing draws to completion, the emphasis has shifted to the planning and initiation of the injurious testing that is needed to create the HIPCs. The WEO is planning to conduct approximately 500 experiments over the next three years to develop the HIPCs. In FY16, a detailed test matrix was developed based on a prioritization of the injuries that have been observed in theater and those variables that are judged to be critical during the conduct of Title 10 LFT&E for vehicles. This planning also included the development of standards for testing, data analysis, and for the creation of the HIPCs. The three primary framing considerations in the development of these standards have been determining the best statistical solution, defining quality measures,



and seeking the metrics that provide the best injury prediction capability taking into account the specific injury mechanism and the injury severity. The definition and refinement of these methods are being guided by applying them to data from initial exploratory injury testing for the lower leg and head-neck body regions. To date, preliminary HIPCs are being developed for the foot-ankle body region as well as for fracture of the basilar skull and cervical spine (Figure 6-5).

Whenever possible, new WIAMan biomechanics data will be transitioned to the RDT&E community as a “spin-out” in order to increase the validity of Title 10 LFT&E prior to the availability of the WIAMan capability. For example, the new HIPC for foot-ankle injuries provides an opportunity to conduct matched-pair testing with the current Hybrid III ATD in order to create an IARC that is more appropriate for UBB than the one currently in use, which is based on frontal car crash loading. This work is nearing completion and will be presented to the LFT&E community in FY17.

In 2013, then SECDEF, the HON Leon E. Panetta, lifted the ban which excluded female Service Members from serving in certain combat positions. The WEO coordinated with members of the WIAMan SSG on the appropriate response to this decision. It was decided to conduct an exploratory biomechanics test effort to determine if there are marked differences in the response of females and males to UBB loading conditions. Leaders from the DHP provided a three-year resource stream for this task and the biomechanics effort began in FY16. PMHS tests have begun in the blast-driven, test rig known as the Accelerative Loading Fixture (ALF). These tests are performed at Aberdeen Proving Ground (APG) by a team of principal investigators from VT, OSU, and WFU. Initially, the tests will be performed using whole-body male and female PMHS under identical loading conditions such that side-by-side comparison can be made both in terms of measured response and observed injury patterns. The results and observations from the initial whole-body testing in the ALF

will be used to define the plan for the latter stages of the exploratory effort. The emphasis during that period will be on investigating the reason for observed differences between males and females, as well as developing a recommendation for the steps that could be taken to use the new WIAMan capability to provide risk assessments that are useful for both male and female Service Members.

### **Status of the WIAMan Purpose-built Instrumented ATD**

In December of 2015, the WEO took delivery of the first instrumented ATD which is designated TD1 (Figure 6-6). The device was developed through a contract with Diversified Technical Solutions Inc., who delivered TD1 early and below the original cost estimate. During FY16, the TD has been used in laboratory tests and blast driven tests in order to assess usability, durability, and how well it replicates the response of PMHS in the military UBB environment (Figure 6-7).

TD1, incorporated improvements to the original WIAMan technical data package (TDP), such as material definitions for flesh and rubber parts, changes to the shoulder structure based on early modelling and simulation results with FEA, removal and correction of interferences in the shoulder/rib complex, and an improved cervical spine based on early testing of the original design. A second TD, known as TD2, was delivered in the fourth quarter of FY16 to accelerate physical testing. TD1 was used to perform 71 whole body tests and 300 component tests for biofidelity and durability. TD2 has completed 20 whole body tests for biofidelity and strength of design. The next phase in the development of the ATD will be the design and fabrication of a Gen 1 TD. The Gen 1 TD will be delivered in FY17 and for the first time will include all on-board data acquisition system (DAS) components. A significant proof of concept effort, including and fabrication and testing necessary to support the Gen 1 TD design, was completed during the third and

**FIGURE 6-6: The First WIAMan Technology Demonstrator, TD1** (Photo courtesy RDECOM)



fourth quarters of FY16. As a result of this work, the leg, pelvis, and lumbar spine of the Gen1 TD are expected to show significant improvements in overall performance and durability. In addition to the design changes for the high priority body regions, modifications to the shoulder/rib structure, femur, femoral head, knee joint, and chest jacket/flesh are also under consideration. These changes will improve integration of the DAS as well as the mass properties of the ATD. As the design evolved through fiscal 2016, periodic updates were made to the TDP. A System Performance Specification document for the S&T project was completed by the WEO in September 2016. This document will guide the remainder of the S&T effort and can be used to support future acquisition activities. Finally, initial procedures were developed and evaluated for certifying that

a WIAMan ATD is in satisfactory condition for use. Approximately 120 tests were performed to develop these procedures, including component level tests for head, neck, thoracic spine, lumbar spine, pelvis, leg and foot components, as well as the whole body system. A refined set of procedures with a final list of test conditions and pass/fail corridors will be developed in FY17 based on the Gen 1 TD design and reproducibility requirements.

### **FEA Model of the WIAMan ATD**

FEA is a numerical analysis technique that can produce a high fidelity approximation of the time-dependent response of complex physical systems under the application of dynamic loads. Therefore FEA has become an essential tool for developing ATDs. Once the ATD FEA model is adequately described and validated against physical test data, it can be used with confidence to perform design studies to rapidly and affordably refine and perfect the ATD design. The description of the ATD must include geometry, the properties of the materials, including models of their response and criteria for damage and failure, as well as boundary and interface conditions. The WIAMan ATD FEA model is shown in Figure 6-8. The geometry of the ATD has been broken down, or discretized, into a mesh consisting of over 1.3 million interconnected elements. Collectively, this mesh describes the physical detail of the ATD including the sensors. When conducting an analysis, the FEA model provides simulated sensor signal outputs that will ultimately be used in conjunction with WIAMan biomechanics knowledge to provide a virtual injury risk assessment.

The FEA capability has been created through a joint effort by the WEO, Corvid Inc., who has created an FEA model suitable for use with their Velodyne solver, and the JHU/APL and WFU who have created a model suitable for use with the LS-DYNA solver. In FY16, the team has focused on the validation of the FEA models against emerging test results for TD1. The WEO validated the WIAMan FEA model for 11 test conditions that were used for injury biomechanics testing.

**FIGURE 6-7: The WIAMan TD1 ATD Has Been Subjected to an Initial Operational Evaluation at ATEC.**  
(Photo courtesy ATEC)



Validation was performed for the whole-body model as well as at the component level for the lower-leg, pelvis, lumbar spine, and the head and cervical spine. Having validated the model, it was used for a number of studies including:

1. Sensitivity analyses for the lower leg, lumbar spine and whole body were conducted to define options for enhancing their biofidelity.
2. High severity simulations were performed to investigate the WIAMan strength of design (SoD) prior to the project's ability to physically test the ATD at these extreme levels. Top areas of design concerns were identified and investigations were conducted to understand the mechanism of damage to help inform a mitigation approach.
3. Component design iterations such as pelvis, femur, lower leg, foot, and shoulder were successfully investigated and new design improvements were identified to inform the Gen 1 TD design. Alternate cervical spine designs to improve biofidelity, removing femur compliant element to improve femur bending biofidelity, and shoulder redesign to improve component stability and strength are a few of the design contributions to improve ATD biofidelity and SoD.
4. FEA modeling was used to verify the proposed ATD certification testing methods including range-of-motion testing and whole body testing to determine if seat and floor inputs can be tested independently.
5. Exploratory simulations were performed to demonstrate the use of the WIAMan ATD within a FEA model for a military vehicle (Figure 6-9). This was a successful step toward transitioning the model for use by the larger RDT&E community.



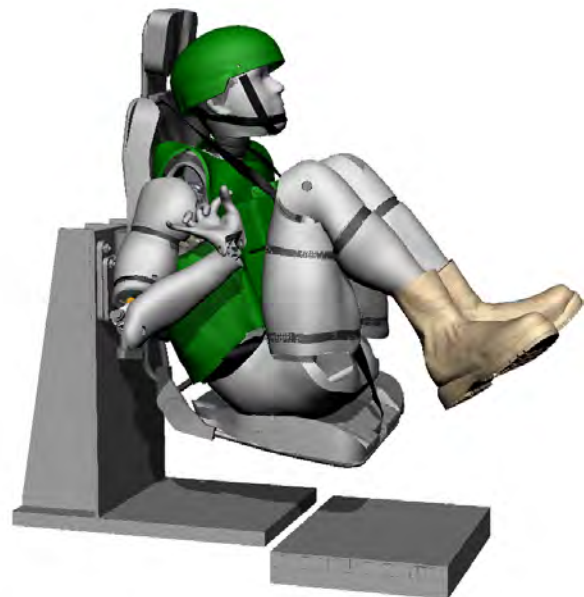
In addition, the FEA model that is used to guide the development of the ATD can subsequently be used to conduct virtual developmental and live fire tests to conceive, refine, and evaluate protection technologies and prototype vehicle designs. The T&E community can use the model to perform pre-test predictions and to assist with evaluating the results of developmental and full-up system live-fire tests. For all of these reasons, the WEO is executing a robust effort to create a valid FEA model of the instrumented WIAMan ATD, use it to guide development, and will transition that model through SLAD to the RDT&E community.

Based on the validation and maturation of the WIAMan FEA model, the WEO has begun to selectively release these knowledge products to the RDT&E community along with detailed user manuals. The WIAMan FEA model is now under evaluation by the SLAD of ARL and by the TARDEC. Reflecting the importance of the FEA work to the WIAMan effort, in January 2016, the WEO co-sponsored the second Workshop on Numerical Analysis of Human and Surrogate Response to Accelerative Loading. Thirty-six presentations were given over the course of this three-day event by participants from government, academia, and industry including delegates from the United Kingdom, Australia, and the Netherlands. This workshop provided an opportunity for the WEO to provide emerging progress on the development of the WIAMan FEA model and WIAMan biomechanics test results. The proceedings of this workshop and the first one held in FY14 are available through Defense Technical Information Center (DTIC). Finally, the WIAMan FEA model provides an opportunity for advanced coordination with the PMs of vehicle acquisition programs. Today, these vehicle programs are already using FEA simulations to assess the survivability of their systems with the Hybrid III ATD. The WIAMan FEA model is fully compatible with the software that is commonly used for these analyses and can be inserted into the analysis stream. The data will provide the PM with an initial understanding of how they

**FIGURE 6-8: FEA Model of the WIAMan ATD.** (Photo courtesy RDECOM)



**FIGURE 6-9: Response of the WIAMan ATD When Used Within a Simulation of a UBB Attack on a Full Vehicle** (Photo courtesy RDECOM)



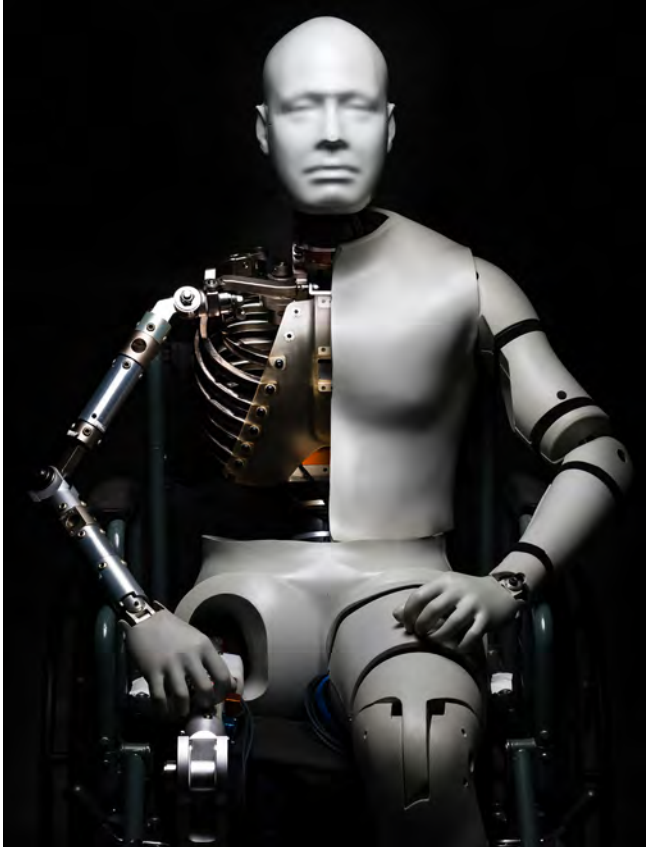


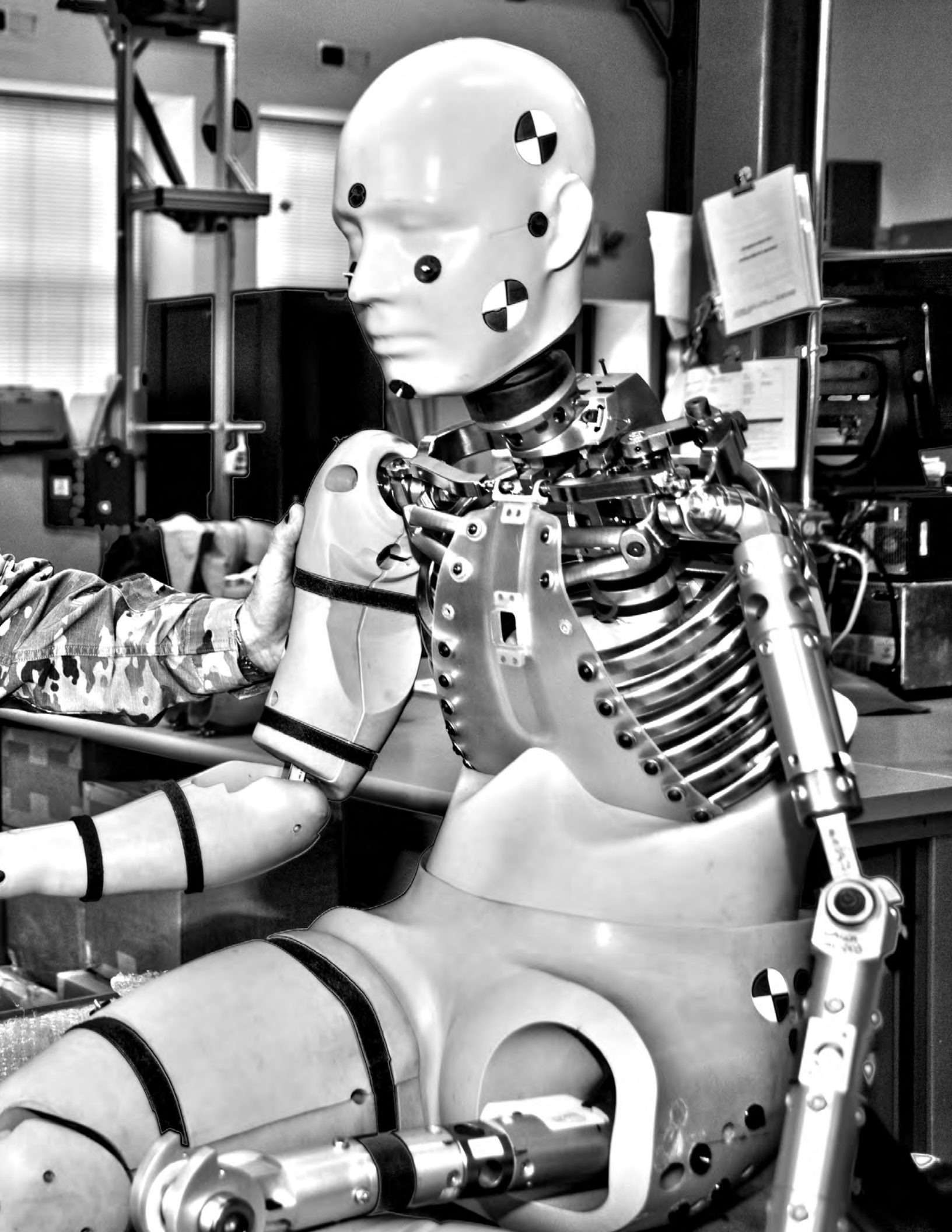
Photo credit: RDECOM and the Diversified Technical Systems Inc.

will be evaluated in the future and at the same time provide feedback to enhance the development of the WIAMan capability. As injury assessment criteria emerge from the Biomechanics program they will be incorporated into the FEA modeling capability which will provide vehicle PMs with guidance well before the introduction of the WIAMan capability into practice.

### Way-ahead and Prospects for the Future

As the WIAMan S&T project continues to march towards a demonstration in FY18 at Technology Readiness Level of six, DOD and Army leaders are considering options for bringing this emerging capability into use. What is clear at this time is that there is a desire to obtain maximum benefit from the technology solution produced in the S&T project being performed by RDECOM. It is also clear that there is a desire to deploy this capability for use in system-level and full-up-system-level testing as soon as possible. Various courses-of-action are under consideration and establishing a program-of-record at PEO-STRI is the top option. The WEO and PEO-STRI have been working since FY15 to establish the foundation for a program-of-record, including the development of a Program Office Estimate (POE), conducting market research (including holding an Industry day in June 2016),

and developing execution strategies and schedules. Ever mindful of achieving the best value for the Service Member, as these future options are considered, Army leadership and the WIAMan team are posing the tough questions; such as how much injury assessment capability is enough? Some of the final answers won't be obtained until the WEO completes the injury biomechanics task and the development of IARCs in FY19, but it is clear that as these knowledge products become available, due diligence will be used to assure that the RDT&E community receives a test capability that meets requirements, is affordable to procure and sustain, and which is suitable for accreditation by ATEC. Based on extensive analyses of the UBB environment, skeletal injuries observed in theater, the biomechanics test results achieved, and the emerging capabilities of the WIAMan TD ATD, the S&T solution will provide a wholesale improvement from head to foot. In addition to laying the foundation for fielding a new test capability, a bright future is envisioned for many of the knowledge products being developed by the WEO. One example is in the study of human response to severe environments where the application of the FEA technique to human descriptions with full anatomical resolution is becoming a reality. To develop valid models of humans, actual response data is needed. The biomechanics data from WIAMan will be invaluable as it will provide insight on both non-injurious and injurious loading conditions for the UBB environment. In fact, the first work of this type has already been performed at WFU (see Snapshot of the Future). Finally, the history of military progress shows that as the S&T community redefines the art of the possible, Service Members are able to better articulate and manage their priorities and requirements for materiel solutions. As the knowledge produced by WIAMan is integrated into the requirements development process, the US Army Training and Doctrine Command (TRADOC) will be in a stronger position to articulate their survivability requirements and to conduct analyses of alternatives. The dividends of all this work will be reaped by Service Members well into the future as fewer and less severe injuries and a better QOL for Veterans and their Families.

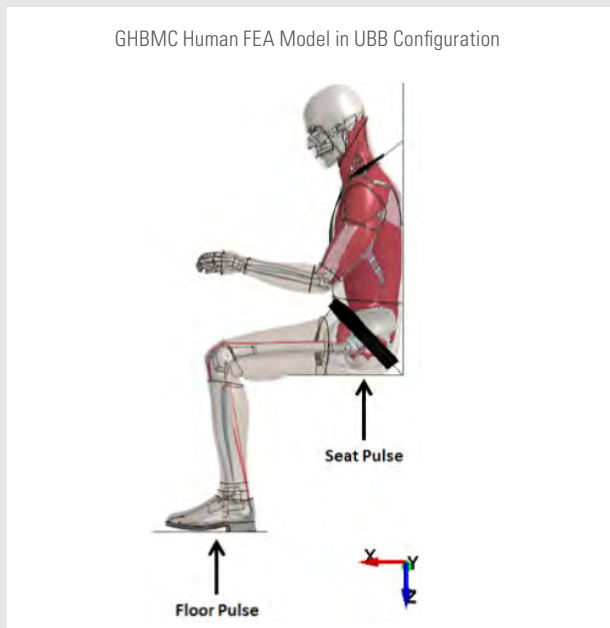




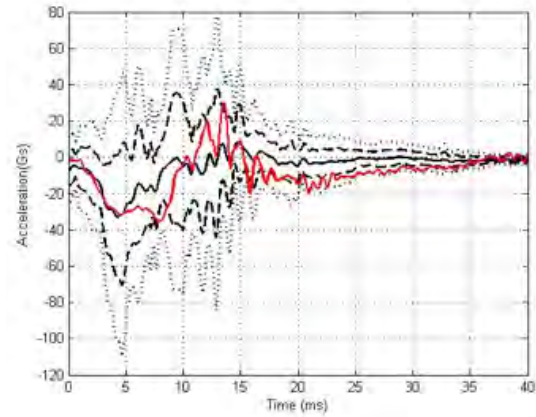
## Snapshot of the Future: WIAMan Impact on the Analysis Tools Which Will Drive Protection and Vehicle Technology

The WIAMan S&T biomechanics task, funded by the DHP, is creating a national treasure; a database on human response to vertical accelerative loading that is unmatched in its breadth, depth and uniformity. In addition to providing the foundation needed to establish the new WIAMan UBB injury assessment capability; it is also precisely what is needed to fuel the development of a next-generation injury assessment capability that employs physics-based modeling of the human body to predict injury risk. Physics based modeling of the human body has been under development within the automotive safety community for some time, and the Global Human Body Model Consortium (GHBM; <http://www.ghbmc.com/>) is a prime example. One of the current limitations for human body modeling for military applications is the lack of experimental data collected under operationally relevant loading conditions. The biomechanical test data collected under the WIAMan project fills that void and provides an invaluable resource to the biomechanics community for the development and validation of human body models.

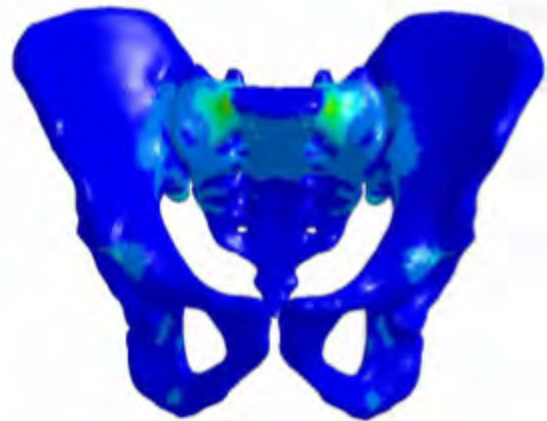
The example below shows the Global Human Body Modeling Consortium (GHBM-M50-O) 50th percentile seated male model, developed by the automotive safety community, being subjected to a simulated UBB



Comparison of Predicted FEA Model Pelvic Acceleration and Biofidelic Response Corridors from the WIAMan S&T Project



Strain Pattern in the Pelvis and Sacrum Predicted by the FEA



exposure. Simulations were performed in LS-DYNA using vertical acceleration pulses applied to the floor and seat to match testing performed by the WIAMan S&T project biomechanics efforts. Pelvic accelerations predicted by the model can be compared against the experimental data from the WIAMan S&T project to evaluate the biofidelity of the GHBM model using an objective rating method. Good agreement was found in the S1 region of the pelvis between the GHBM-M050-O FEA model and the WIAMan experimental data. Another physics-based human body modeling effort using WIAMan biomechanics data is CAVEMAN,

a development effort sponsored by the US Marine Corps PEO Land Systems AutoCell activity. The work is being performed by CORVID Inc. The CAVEMAN model was developed primarily for use in studying the effects of UBB loading on mounted Service Members. Like the WIAMan ATD, the CAVEMAN model is built to represent the anthropometry of the 50th percentile male soldier. Preliminary simulations performed with the CAVEMAN FEA model, have shown good correlation to the WIAMan BRCs. This effort will produce a comparison between the response of CAVEMAN, the current Hybrid III ATD, and the future WIAMan ATD in a full vehicle simulation.

Although these two examples represent the first steps in applying WIAMan S&T biomechanics data to physics-based modeling of the human, they have increased confidence that it will be feasible to use such simulations to better understand the human response to vertical loading, which will improve our ability to predict fractures and other injuries that Service Members have suffered. Someday, when such models have been validated against both biofidelity and injury data from WIAMan, they may be used to identify injury risks to mounted Service Members, and to support the precision design of improved protection technology including active protection systems and vehicle structures.

The Mesh of the CAVEMAN Physics-based Human FEA Model







CHAPTER 7:

# DOD BLAST INJURY RESEARCH PROGRAM ACCOMPLISHMENTS



**T**he PCO's EA support mission is to coordinate DoD blast injury research investment and leverage expertise in order to develop strategies that prevent, mitigate, or treat blast injuries. To inform the EA of accomplishments throughout the blast injury research community, the PCO requested data from DoD organizations engaged in medical and nonmedical blast-related research at the end of FY16. The PCO received over 140 responses from 32 organizations, summarized in the chapter that follows. These accomplishments are organized by the DoD Blast Injury Research Program's key program areas: Injury Prevention, Acute Treatment, and Reset. Each accomplishment adds to the knowledge base for blast injury research and refines the strategies that prevent blast injury or allow injured Service Members to RTD and maintain an active lifestyle.

### **Program Area: Injury Prevention**

Research on blast injury prevention considers the entire spectrum of potential injuries, from primary to quinary. The design of prevention systems requires an understanding of the mechanism of injury; thus, significant research efforts are focused on replicating blast exposure conditions in the laboratory and determining blast injury mechanisms using animal and computational models. Researchers are also collating clinical and theater data to analyze blast threats and assess PPE performance. These data are currently being used to establish safety thresholds for human exposure to blast, support the design of protection systems, strengthen guidelines for the safe use of weapon systems, and identify biomarkers and potential treatment targets. Findings are shared between the military and civilian research and development communities to encourage greater use and availability of protective measures against blast events in both sectors.

## **Aeromedical Evacuation**

### **Evaluation of the Aeromedical Evacuation in Rat Blast Models of TBI and Polytrauma**

Research at the Naval Medical Research Center (NMRC) includes assessing appropriate timing for altitude transport of casualties based on physiology, regional organ perfusion, inflammatory markers, tissue damage, and mortality in rat blast polytrauma models. Investigations include evaluating the effects of low atmospheric pressure associated with aeromedical evacuation during either standard (three days after injury) or delayed (day seven-14) transport of injured rats. Additional research efforts will evaluate adverse effects of exposure to environmental stressors associated with aeromedical evacuation (e.g., vibration) on TBI/polytrauma casualties.

### **Aeromedical Stabilization Evacuation System Prototype**

Service Members who are severely injured in the field with TBI and/or spinal cord injuries (SCI) often need to be evacuated in order to receive the necessary medical care; however, the aeromedical evacuation environment itself represents a potential for increased injury due to the motion and turbulence associated with flight. This Phase III project was funded through the OSD's Small Business Innovation Research (SBIR) program (topic number OSD09-H13, "Aeromedical Stabilization and Evacuation of Traumatic Brain and Spine Injuries"). The problem as defined in the solicitation is the need for a lightweight, component based system that will provide cervical spinal splinting and traction, and thoracic/lumbar splinting as needed. The Aeromedical Stabilization and Evacuation System (ASES) concept consists of three subsystems including a Patient Support Platform, a Comfort Mat System (CMS) and a detachable Aeromedical Equipment Module (AEM).



A

R

C

H

E

V

P

U

Airway

Head tilt chin lift  
Observe airway to ensure there  
is nothing blocking it

Rate, Rhythm, Quality  
Roll and Cradle the Back

Pain

Unresponsive

PRICE

MOUNTAIN

ISAF  
OPERATION ENDURING FREEDOM

MY

The awardee, Techshot Inc.'s ASES, is a modular, scalable, mobile treatment system that provides splinting and cervical traction to securely transport patients. The ASES prevents secondary injuries, hypothermia, and bedsores during transport from the battlefield to hospitals stateside. The optional AEM provides a power and oxygen buss for aeromedical and Critical Care Air Transport (CCAT) equipment to serve the patient's needs as well as surrounding patient's needs without piling bulky equipment dangerously above the patient. This system provides a stabilization and traction platform solution for aeromedical evacuation with CMS using heated alternating pressure air bladders or gel technology to prevent pressure sores. The prototype system is designed to minimize motion, including torsion, on evacuated subjects with SCI, TBI, and polytrauma during fixed wing and rotary medical evacuations. Airworthiness testing of this prototype is ongoing at the US Army Aeromedical (USAARL) and Air Force Research Laboratories (AFRL). Prior to use within the MHS, the ASES will still need to be evaluated based on global performance criteria, such as compatibility with current En Route Care transport platforms, patient comfort and ergonomics, maintenance and durability, implementation, functionality, manufacturability, and cost constraints.

#### **Joint-Force Aeromedical Transport Litter Immobilization and Stabilization Prototype**

Service Members who are injured in far forward locations often need to receive medical treatment during transport including aeromedical evacuation. Because of challenges associated with administering medical care within a moving environment, including the potential for exacerbating current injuries, treatment provided during both ground and air transport must be

improved to address proper immobilization, shock and vibration isolation, injury site access, and medical equipment storage. As part of the SBIR program, the Cornerstone Research Group, Inc. received funding to develop a prototype with the capability to reduce the impact of the moving environment on patient physiology with the goal to prevent pressure ulcer development, hypothermia, and secondary injury associated with TBI or SCI instability. The Aeromedical Transport Litter Immobilization and Stabilization (ATLIS) Prototype includes the Spinal Immobilization System (SIS) and the Patient Stabilization Platform. The SIS contains a head and neck immobilization device, a cervical immobilization and traction device, and a cervical immobilization collar. The Patient Stabilization Platform is comprised of three subsystems including a mattress with a rigid transport litter, a restraint system, and a fluid management system. The ATLIS prototype aims to expand life-saving interventions by integrating treatment-compatible, reduced-footprint devices in order to enhance patient treatment, transfer, and monitoring capabilities and improve caregiver casualty management efficiency. It is hoped that fostering advanced medical treatment closer to the battlefield will reduce patient transport time, minimize patient transport system weight, and improve dynamic performance. Currently, airworthiness testing of this prototype is ongoing at the USAARL and AFRL. Prior to use in the MHS, the ATLIS Platform will still need to be assessed based on global performance criteria, such as compatibility with current En Route Care transport platforms, patient comfort and ergonomics, maintenance and durability, implementation, functionality, manufacturability, and cost constraints.



### **Blast Exposure Analysis Naval Health Research Center Data and Analysis Support to the Joint Trauma Analysis in the Prevention of Injuries in Combat Program**

The Naval Health Research Center (NHRC) is intimately involved in supporting the JTAPIC Program through the provision of the coded injury information that is associated with each combat event where a Service Member is injured. The NHRC provides a weekly analysis of all combat casualties occurring in the previous seven days during overseas contingency operations to the JTAPIC Program Office. For each wounded Service Member, the medical data obtained from NHRC's Expeditionary Medical Encounter Database (EMED) is thoroughly reviewed at NHRC and a clinical profile is developed describing a casualty's injury characteristics. Each casualty's injuries are then coded on various diagnostic and injury severity taxonomies by registered nurses. In addition to injury analyses conducted at NHRC, these detailed clinical profiles are then made available to the JTAPIC partnership for additional analysis where tactical data (such as weapon type, explosive weight, strike point) are matched to the injury profiles. This mapping of medical to tactical data allows vehicle and PPE developers to design targeted modifications to improve vehicles and PPE, thereby reducing the frequency and severity of injury. Because of the common requirement for medical data, NHRC participates in nearly every JTAPIC partnership analysis. In FY16, there were 21 JTAPIC products that used medical information provided by NHRC. In addition to supplying coded medical data, NHRC actively participates and produces medical analysis products for JTAPIC. During FY16, NHRC provided analysis for six products and acted as lead organization on three. The immediate availability of medical data and the provision of analysis allow the intelligence community to monitor the effectiveness of the insurgency threat's evolution and permits rapid responses

to identify and defeat new and emerging threats—directly reducing casualty rates.

### **Development of Occupational Standards for Repeated Blast Exposures**

This research funded by JPC-5/DHP, evaluates neurocognitive and vestibular data gathered from Service Members previously exposed to IEDs. Researchers in the Neurotrauma Department at NMRC, in collaboration with clinical and scientific partners (including the WRAIR, USUHS, NINDS, National Institute of Nursing Research, the James J. Peters VA Medical Center, the UVA School of Medicine, and NICOE) have also initiated a series of studies to develop occupational exposure standards for repeated exposure BOP events to predict human safe blast exposure limits in terms of blast magnitude, number, frequency, and between-blast latency. Assessment modalities include neurocognitive (neuropsychological), functional (neuroimaging, magnetoencephalography), and physiologic (known and novel biomarkers) changes. The aim of these studies is to develop predictive models/algorithms of all data for use in the development of an occupational standard for use by operational planners. Research efforts will also explore potential interventions to mitigate the acute, subacute, and/or chronic neurological adverse effects of TBI and evaluate the cumulative deleterious effects of blast exposures on the brain to define exposure limits and standards to mitigate this risk among Service Members.

### **Development of Deformation and Failure Criteria for Human Femoral Bone under Ballistic Loading Rates**

An accurate understanding of fracture in human bone, under complex loading scenarios, is critical to predicting fracture risk. Cortical bone, or dense, compact bone, is subject to complex loading due to the inherent multi-axial loading conditions, which are also influenced by the anisotropy of the microstructure. When determining critical

fracture parameters, bone is traditionally idealized as isotropic. This work presents a method to examine rate-dependent mode mixity associated with cortical bone crack initiation. Four-point bend experiments have been conducted on cortical femoral bone samples from three human donors at quasi-static (slow), intermediate, and dynamic loading rates. Digital image correlation was used to obtain full-field displacement maps, at the crack tip, during the experiments. An over-deterministic least squares method was used to evaluate Mode I (opening) and Mode II (shear) stress intensity factors (SIF) for fracture initiation at slow (10.2 MegaPascals-meter<sup>1/2</sup> per second), intermediate (15 MegaPascals-meter<sup>1/2</sup> per second), and high (4.54 MegaPascals-meter<sup>1/2</sup> per second) SIF rates. Results show that under dynamic loading, the critical SIF in Mode I, assuming material anisotropy, is approximately 50 percent lower than fracture toughness assuming isotropy.<sup>27,28</sup> Additionally, critical Mode I and II SIFs had the lowest values at the highest rate of loading examined, decreasing to one third of the values shown under quasistatic loading. Crack growth in the low and intermediate SIF rates appears to be Mode II dominant, and shows a transition to completely mixed-mode at the high rate of loading. This suggests that the conventional assumption of isotropy is a conservative estimate, at low and intermediate rates, but overestimates fracture strength at dynamic rates. These fracture thresholds and mechanistic understandings can be used to develop fracture initiation criteria from defects and micro-cracks in bones of the lower extremities. Fracture initiation criteria can be implemented in large scale computer codes to predict bone fracture when the Service Member is exposed to military-relevant, high rate, blast and ballistic loading. These studies will promote development of novel lower extremity protection concepts to mitigate fracture injuries from blast and impact loading.

### **Assessed Injury Risk from Blast Exposures Transmitted to Gunner/Assistant Gunner**

The Blast Overpressure-Health Hazard Assessment (BOP-HHA) version 2.0 software analyzed data collected during tests conducted at Aberdeen Test Center (ATC) in June 2016. This quantitative risk assessment, performed by the Army Public Health Center, characterized blast exposures produced by combustion of the propellant when rounds were fired by the M3E1 Multi-Role Anti-Armor/Anti-Personnel Weapon System (MAAWS) and yielded hazard severity and probability estimates for the gunner and assistant gunner firing under ten conditions involving different types of ammunition, round conditioning temperatures, and firing postures. Results of both BOP and impulse noise tests were used to determine the maximum number of rounds that gun crewmembers could fire without incurring significant injury risk for this new weapon system. Test results were used to establish standard operating procedures that will reduce injury risks to Service Members/operators firing the M3A1 MAAWS. The M3A1 MAAWS is being developed to become the next generation Carl Gustaf M4—a lighter weight, more tactically versatile replacement for the system currently being used. BOP-HHA software was developed by USAMRMC to characterize occupational exposures sustained by personnel firing weapons or detonating explosive devices. A variant of the INJURY software developed by JAYCOR Corporation (now L-3 Corporation), BOP-HHA uses an algorithm based upon experimental data collected from over 1,000 exposed specimens over a period of over 20 years and includes a biomechanical model of the thorax that estimates the amount of “push” or mechanical work imparted to the thorax by a blast pressure wave. The calculated work value is used to estimate the risk of lung injury expressed as risk coordinates (hazard severity and probability) as described in Army Regulation 40-10. BOP-HHA is the primary methodology used

by Army Public Health Center to assess injury risk from the non-auditory component of blast.

### **Assessed Injury Risk from Blast Exposures Transmitted to US Marine Corps Gun**

The BOP-HHA version 2.0 software analyzed data collected during tests conducted at ATC in May 2016. This quantitative risk assessment, performed by the Army Public Health Center, characterized blast exposures produced by combustion of densified propellant when rounds were fired from the M724A1E1 Shoulder-launched Multipurpose Assault Weapon (M724A1E1 SMAW) and yielded hazard severity and probability estimates for the gunner and assistant gunner firing under three conditions involving different propellant mixtures and round conditioning temperatures (Figure 7-1). Data collected from this test will guide decision making during development. Specifically, results of toxic gas sampling and the BOP analysis were used to determine the maximum number of rounds that crewmembers could fire without incurring significant injury risk from this new system. Test results were used to select a densified propellant mixture that will emit less BOP, permit firing from within enclosures and confined spaces, and reduce injury risks to Service Members/operators firing the M724A1E1 SMAW.

### **Blast Dosimeter**

Researchers with L-3 Applied Technologies, Inc. received funding from the FY13 Army Rapid Innovation fund to develop a low-power soldier-worn blast dosimeter to estimate blast exposure dosages and correlate exposure to injury probability. This product was developed under the umbrella of the Environmental Sensors in Training Program (ESiT) and in concert with the Brain in Combat Technology Enabled Capability Demonstration/ Science and Technology Objective with the aim of enhancing combat medic capacities in far forward environments. A chest-mounted dosimeter was developed to measure BOP, body orientation, linear acceleration, and angular



**FIGURE 7-1:** Pictures from Adapting SMAW to Urban Fighting Again, A Densified Propellant for Firing from Enclosures (Credit: Diana Bragunier & Matthew J. Sanford Marine Corps Gazette • October 2015)

velocity. Concussion and lung injury risk due to blast exposure are calculated using onboard algorithms based on previously validated blast dose response curves and lung injury severity models. The dosimeter provides immediate visual feedback of calculated injury risk and stores data from multiple exposures for



downstream analysis. Probability of injury due to exposure can be used as decision aids by medics and unit leaders when determining if a Service Member needs to be removed from the battlefield for additional assessment and treatment. The prototype dosimeters were subjected to laboratory blast and environmental testing conditions required to produce a final deliverable prototype. Final prototypes were evaluated in open-field blast environments and compared to laboratory blast sensor technologies. At the completion of the project, L-3 Applied Technologies, Inc. delivered prototype blast dosimeters with supporting software for additional field testing by DoD researchers.

### **Accelerative Loading Workshop**

The ARL hosted a workshop on “Numerical Analysis of Human and Surrogate Response to Accelerative Loading” in January 2016. The workshop was co-sponsored by the WEO and the Blast Protection for Platforms and Personnel Institute. Approximately 170 attendees, representing nine countries, 14 universities, 13 industrial partners, and numerous organizations throughout the DoD and other government agencies, participated in this three-day event. The workshop addressed the numerical analysis tools and methods available to simulate and investigate the response of vehicle occupants to accelerative loading induced from blast events, with an emphasis on UBB. The objectives of the workshop were to explore the scope of current research activities, highlight recent advances in models and techniques, document the capabilities of existing numerical analysis tools, extract knowledge and insights gained from using these tools, and identify technical gaps and numerical tools for critical future needs. The workshop provided a venue for the presentation of science and engineering projects that reflected the latest innovations in state-of-the-art technologies for characterizing and simulating the human response to typical accelerative loading conditions seen in the field. The 36

technical presentations highlighted current capabilities in computational modeling of the human body. Focused discussions addressed the assessment of existing injury criteria; methods for quantifying model validation; scaling techniques for modeling the broad anthropometric spectrum of the Service Member population; and novel imaging techniques for documenting injury. Discussions also helped to identify gaps in the current research, and set short-term goals for continued model development, validation, and application. The Proceedings of the workshop are in review, and will be published in FY17. This workshop provided an opportunity to share the latest innovations in human body modeling with experts from around the world. It also helped to initiate new collaborations in biomechanical modeling and testing to improve ARL’s knowledge of injury mechanisms and thresholds. This knowledge will help advance protective technologies for our Service Members and reduce the incidence of injuries related to blast and ballistic impacts.

### **Anthropomorphic Blast Test Device Validation and Transition**

L-3 Applied Technologies, Inc. received funding from the DMRDP managed by CDMRP for a project to validate the Anthropomorphic Blast Test Device (ABTD) for performing BOP-HHA testing and analysis. Since this award in July 2016, the team has been working in close collaboration with the testing community represented by the US Army Public Health Command, ATC, and Yuma Testing Center. As an integrated device, the ABTD enables the biofidelic collection of auditory and non-auditory data simultaneously from the same blast for the assessment of impulse noise and blast lung injury. A simulation study of potential differences in collected measurements between current Blast Test Devices (BTD) and ABTDs for the purpose of predicting lung injury and continuing to update software has been completed. Auditory data



Photo credit: Justin Connaher/US Air Force

will be collected by mounting sound gauges on top of the ABTD at the ear location for impulse noise hazard assessment based on MIL-STD-1474D “Department Of Defense Design Criteria Standard Noise Limits”,<sup>29</sup> and pressure sensors will be mounted at the chest elevation to collect thorax loading data for blast lung injury assessment using the normalized work algorithm that is incorporated in the BOP-HHA software. Using field test data and additional computational analysis supplied from Computational Fluid Dynamics (CFD) simulations and other existing data archives, the normalized work algorithm will be adjusted for the ABTD BOP-HHA software. The software will be re-written using a currently supported programming language to meet government informational assurance, and the package will be prepared for ATEC for verification, validation, and accreditation. The proposed system addresses an important area of research into the blast injuries of Service Members, and this device will assist in designing mitigation techniques for blast injury.

#### **Analysis of Fragment Related Injuries**

Soldier Systems Branch (SSB), Capabilities Development Integration Directorate submitted a RFI to JTAPIC for an analysis of fragment related injuries to the thorax, abdomen,

neck, and upper extremities received by Army personnel wounded in action (WIA) by explosive threats while operating outside the confines of a defended installation. The purpose of the request was to obtain a baseline of injuries for future assessments of the effectiveness of the Army Ballistic Combat Shirt (BCS), a subsystem of the Soldier Protection System (SPS). The BCS is designed to provide soft armor protection at a lighter weight than previous soft armor solutions. JTAPIC developed a product<sup>30</sup> depicting color-coded wound mapping that identified specific injuries inflicted to areas for which the BCS provides soft armor protection. Additionally, the product included photographs and damage analysis of recovered items of PPE associated to the casualties in the study population. The analysis also included characterization of fragments along with a modeling and simulation component to predict the probability of serious or greater severity of injuries inflicted to the thorax by the most common fragment mass, comparing predicted injury severity based on BCS protection to that without BCS protection. In the future, SSB plans to request updates of injuries to Service Members wearing the BCS protection to compare to this baseline product. This report provides a baseline of fragment related injuries that will enable analysts to compare to injuries received to Service Members wearing the BCS.

#### **Environmental Sensors for Blast Overpressure in Military Training**

In 2013, the Army Resources and Requirements Board (AR2B) determined a need for additional capability in the protection of military personnel from neurotrauma following exposure to explosive blast or accelerative/ decelerative force. AR2B decision making yielded a TRADOC Tasker for a holistic review of environmental sensors in training, and USAMRMC was designated as the lead for that review. The USAMRMC ESiT program was

established with the purpose of informing technical requirements for environmental sensors and methodology for employment of those sensors in select training events. Laboratory and field evaluations of available sensor technologies were conducted for mortar, artillery, grenade, breaching, combatives, and airborne training units. The ESiT Program also supported and closely monitored other military field evaluations that included environmental sensors as well as measures of brain dysfunction. ESiT produces technical reports which may be requested from the DTIC website, published manuscripts, and conference presentations to document program methods and findings. Complementing the TRADOC Tasker, the Executive Order for Improving Access to Mental Health Services for Veterans, Service Members, and Military Families yielded the NRAP (2013) which stipulated an immediate action to “determine whether point of injury blast and impact sensors can be correlated to mechanism and severity of injury.” Going forward, the most informative ESiT field studies are those that combine wearable sensors with acute measurements of brain function. Based on evidence to date, from ESiT and other directly relevant studies and programs, wearable environmental sensor capability has proven to be of critical value for research on neurotrauma in military environments. Routine use of effective sensors, beyond research, is expected to be an important future capability. The envisioned end state of the ESiT Program is wearable sensors for recording environmental exposures in select training environments and making these data available for use by medical providers to inform clinical decisions. The envisioned end state of the ESiT program is wearable sensor capability for recording acute environmental exposures in select training environments and making these data available in an integrated system for use by medical providers to inform clinical decisions. In

addition, in the end state a reduced version of sensor data would be suitable for archiving, recording chronic environmental exposures across a Service Member’s time in uniform.

### **Warrior Health Avatar Technology**

Personalized medicine has the potential to create customized healthcare with medical decisions and treatments tailored to the individual patient. In the last few years remarkable progress has been achieved in personalized medicine, wearable physiological and activity sensors, mobile computing, bioinformatics, and computational medicine; however, there remain few objective measures of the health status of a deployed Service Member. Furthermore, in spite of significant progress in wearable, non-invasive biomedical sensor technology, which can collect large amounts of physiological, physical activity, and environmental data, there are limited established methods to utilize this data in a predictive fashion. Therefore, there is great interest in developing technology that can be used in the field to noninvasively measure current health status and also predict future changes in the health status of an individual. To begin to address these concerns, the DoD SBIR program funded three Phase I projects in response to the FY16 topic “Warrior Health Avatar.”

**1. Vigilant Cyber Systems Inc.** received funding for the Phase I SBIR project titled “Vigilant Warrior Health Avatar.” The goal of this project is to develop a simulation framework and physiology based modeling tools of a Service Member’s body that could enable definitive assessment of health status, physical and physiological performance, as well as physiological responses to various injuries including blast waves, ballistics, and blunt impacts. The system will collect physiological data from wearable sensors and convert this information into audio and visual representations of the health status of the





individual. The simulation framework and user interface will be designed to be intuitive and easy to interpret. Because of their complexity, the models and software tools will first be developed on conventional computers with the ultimate goal to transition to mobile computing platforms. The initial stages of the project will focus on formulating and designing the simulation framework, its key functionalities, main components, communication with wearable sensors, and the user interface. The Vigilant Warrior Health Avatar System will enable Service Members to assess their own health status, permit medics and command leadership to assess individual and unit health status, and allow scientists to study the health of Service Members to improve models of Service Members' health.

**2. CFD Research Corporation Inc. (CFDRC)**

received funding for the Phase I SBIR project titled "Personalized Warrior Health Avatar." The goal of this project is to design, develop, demonstrate, and deploy the "Warrior Health Avatar," a simulation framework and physiology based modeling tool of a human body that enables a definitive assessment of the individual's current health status, physical and physiological performance, and possible injury trajectory. The Warrior Health Avatar will be developed as a user friendly, personalized "App" on mobile platforms that collects and visualizes data obtained from wearable monitoring sensor systems for use by Service Members, Veterans, and medics as well as engineers and scientists involved in Service Member protection and combat casualty care. The platform will enable the user friendly setup of an individual's body anthropometric parameters and basic physiological vitals. Existing computational modelling tools will be used to create quick and interactive simulations of human physiological responses to common environmental stressors, physical activities,

and injuries. Overall, capabilities such as the Warrior Health Avatar will help the DoD reduce healthcare costs, encourage a proactive role in an individual's health, and ensure Service Members' fitness.

**3. Chimaera Science, LLC** received funding for the Phase I SBIR project titled "Warrior Shadow: Holographic Health Avatar for Predictive & Preventative Medicine."

The purpose of this project is to develop a demonstration-grade prototype of a modeling and simulation tool that translates raw physiological data into a visual, holographic representation that can be experienced via mixed reality. This tool will combine physiological data derived from wearable, biometric sensor technology with personalized characteristics such as past health records in order to develop individualized predictions of responses to common battlefield injuries and outcomes of specific medical treatments. This integration of physiological measurements and personal characteristics with information visualization and predictive modeling and simulation technologies can be leveraged to support immediate care on the battlefield as well as long-term predictive and preventative medical interventions.

**Physics and Physiology Based Human Body Model of Blast Injury and Protection**

Blasts from IEDs are one the most common causes of combat injuries in recent military operations; however, there is a limited understanding of blast injury pathways including biomechanical injuries caused by the direct effects of pressures penetrating the body, flying debris, body translocation in air, and impact on hard objects. Therefore, anatomically consistent human body model and computational tools for modeling blast physics coupled to human physiology and biomechanics may help to better understand blast injuries, interpret experimental

data, and develop improved protective armor, diagnostics and medical treatment procedures. As part of the FY14 DoD SBIR program, CFDRRC received funding for the Phase I SBIR project titled “Physics and Physiology Based Human Body Model of Blast Injury and Protection.” The overall goal of this project is to develop, validate, and demonstrate a fast anatomy and physiology based computational tool, and a human body model for assessment of explosion blast injury loads, body responses, injury mechanisms to vital organs, casualty estimation, and evaluation of protective equipment. As part of the follow-on Phase II project, researchers at CFDRRC are currently investigating ways to improve the individual model components, validate the models using experimental data, and integrate these models into a user friendly software tool. The technology developed has immense potential application in military medicine including the development and evaluation of protective armor and equipment, characterization of blast events, development of blast dosimeters and diagnostics, and improvements in treatment of blast injury casualties.

## Injury Models

### **Development of Occupational Exposure Limits Governing Exposure to Multiple Blast Events**

The emergence of evidence linking multiple mTBIs to progressive, long-term debilitation, neurodegeneration, and the persistence of injury symptoms in some blast casualties diagnosed with mTBI (e.g., PCS) has prompted concern over the cumulative deleterious effects of blast exposures on the brain and the need to define standards to mitigate this risk among Service Members. At present, there are no set guidelines for blast exposure limits in military personnel in combat or training operations. Most blast exposures yield mild concussions or subconcussive

disruptions which are difficult to diagnose, are inconsistently and somewhat broadly defined, and are often indistinguishable from the symptoms of PTSD. Consequently, it is estimated that 80 percent of the TBIs occurring among Service Members deployed in Iraq or Afghanistan between January 2003 and October 2006 were undocumented. As part of a multi-pronged research effort, investigators at WRAIR and NMRC are using laboratory rats to address fundamental gaps in knowledge regarding the cumulative effects of blast exposure on the CNS by exploring the impact of multiple blast exposures of varied number, frequency, and intensity on short-, intermediate-, and long-term sequelae. Using a combination of neurobehavioral, neurobiological, and histopathological assessments in a well-characterized experimental model of blast injury in rats, the cumulative disruptive effects of one to five daily blast exposures of mild to moderate severity are being evaluated to identify scaled injury thresholds and neurobiological underpinnings as a step toward defining occupational guidelines and standards for Service Members exposed to blast. As a practical matter, since this research objective is best accomplished under experimental conditions in which other blast-sensitive organs, notably the lung, are not overtly injured, and the potential cumulative effects of repeated BOP exposures on the lung have not been investigated, the initial thrust of this project has been to define exposure conditions in an advanced blast simulator (ABS) under which brain injury can be studied unaccompanied by blast-induced lung contusion and hemorrhage. Research completed to date reveals that lungs are largely contusion and hemorrhage-free following repeated frontal and side-oriented exposures to blast intensities ranging up to 16.5 pounds per square inch peak amplitude (6-8 milliseconds positive phase duration), and



thus provides the defined scaled conditions under which brain injury investigations are now proceeding. These characterizations are yielding great insight into scaling issues experienced in laboratory experimental efforts to predict and mitigate the risks of mTBI in Service Members.

### **Primary Blast Injury Criteria for Animal/Human TBI Models using Field Validated Shock Tubes**

Animal models have been critical to understanding the relationship between blast exposure and mechanisms underlying observed brain injury. Despite significant advances in blast injury animal models, the ability to translate the observations in the animal models to brain injuries observed in humans is less understood. NJIT is a key participant in the DTTI between the US and India, and they have received funding to support this study from the Psychological Health/Traumatic Brain Injury Research Program (PH/TBIRP) managed by

CDMRP. The research team at NJIT works collaboratively with researchers within the Ministry of Defence, India and the DoD to strengthen understanding of the effects of blast TBIs in animal models. In addition, researchers will work to translate the findings of blast injury in animal models to humans through the development of a human Brain Injury Criterion (hBIC). In the initial stages of this work, the team at NJIT has begun to establish master dose response curves for BOP exposure in rats, mapping probability of survival over a range of field-relevant BOPs. In order to build and validate the hBIC, data from this effort are shared with researchers at BHSAI, WRAIR, NRL, as well as with collaborating INMAS-DRDO, DIPR, and ITBRL. This collaborative effort will facilitate the standardization of blast injury animal models and will increase knowledge regarding the association between BOP and TBI. A better understanding of the mechanisms of blast-induced TBI will contribute to the development of effective PPE designed to



Photo credit: SrA Justyn M. Freeman/US Air Force

prevent or mitigate TBI and to the creation of tools to rapidly screen and diagnose Service Members involved in potentially concussive events.

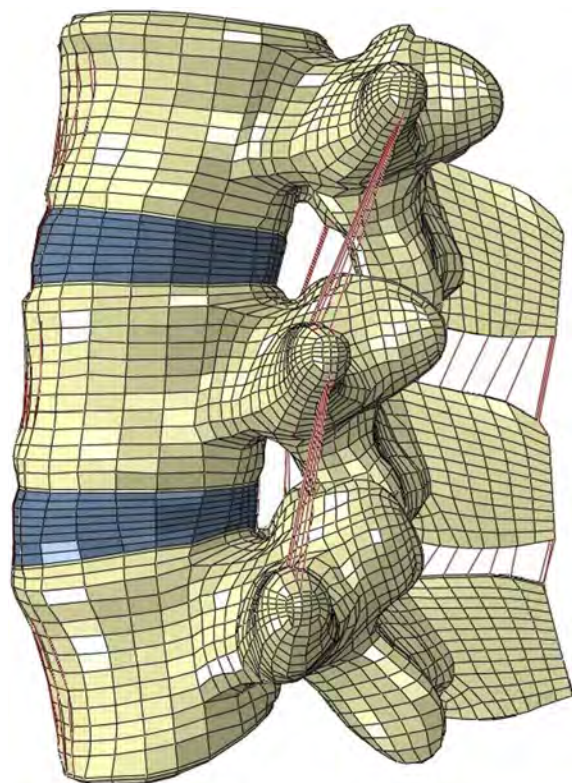
### **Development and Characterization of In Vivo Models of Explosive Blast-related Spinal Column Injury**

In the recent overseas conflicts, OEF and OIF, the incidence of traumatic orthopedic injuries is only secondary to that of TBI. Of the total number of patients sustaining wartime orthopedic injuries, 78 percent have been caused by an explosive blast. Among orthopedic injuries, Joint Theater Trauma Registry data show that spinal injuries represented about 9 percent of all combat related injuries in OIF between 2002 and 2006. In addition, 10 percent of patients treated for TBI at the National Naval Medical Center and WRNMMC have also been diagnosed with spinal column injuries; more than 50 percent of these injuries were due to blast. The use of body armor is likely to affect the pattern of spinal injury, as we see a unique concentration of lower lumbar burst fractures in the ongoing military conflicts. However, it is difficult to systematically characterize these injuries and the associated complications without a reproducible animal model.

The Spine Blast Program at USUHS was established through funding from the DMRDP managed by CDMRP to develop animal models to investigate the effects of non-penetrating blast trauma on the spinal column including the neurologic, osseous, cartilaginous, and soft tissue components (Figure 7-2). To accomplish this goal, the program developed a rat animal model of blast-related non-penetrating spinal column injury with the objective to explore the impact of blast on spinal column integrity in order to aid in the characterization of injury and refinement of treatment options. Briefly, rats were exposed to free field primary blast of various intensities to define injury thresholds

for mild, moderate, and severe orthopedic trauma. A specialized blast wave generator tube that had been previously constructed and validated using a swine model was scaled down to a rodent model and used to generate the free field blast.<sup>31,32</sup> Rats were provided a Kevlar shield that protected the axial skeleton from direct blast trauma. After BOP exposure, the rat spinal column was harvested for biological evaluation using Luxol fast blue and hematoxylin and eosin (H&E) histology for signs of disc degeneration. No fractures were seen as the spine was not likely to have fractured from primary blast with a rigid structure for exposures used in this model. Analysis of the samples is currently in progress and includes: measurement of the expression profiles of cytokines such as interleukin (IL)-1b, IL-6, IL-8, matrix metalloprotease (MMP)-1, MMP-3, MMP-13, and Aggrecan in intervertebral discs using quantitative polymerase chain reaction (qPCR) to identify signs of early degenerative disc disease; completion of myelin staining

**FIGURE 7-2:** Diagram of the Articulated Lower Lumbar Spinal Column



of the spinal cord to determine if there was any noticeable damage to the spinal cord; chromosome sequencing to create genomic signatures; and collection of the final qPCR and luminex data. Together, these data sets suggest that inflammatory pathways are activated in and about the spinal column that may influence overall performance of healing and recovery providing highly unique insights into the events occurring early after blast injury. Additional work has been completed employing a Finite Element Model (FEM) and a Mounted Blast Scenario in order to provide insight into the effect of different blast scenarios on the spinal axis and potential improvements in blast resistant vehicle design. Understanding the injury biomechanics and biology associated with blast will assist in the development of early diagnostic and therapeutic strategies to improve clinical management of the blast-related spinal injury.

#### **Prevention of Blast-Related Injuries**

Researchers at WSU received funding from the PH/TBIRP managed by CDMRP to conduct a study to determine the cause of mTBI due to BOP and, if possible, determine the human tolerance to BOP. The purpose of this study is to determine the specific mechanisms of injury in primary, secondary, and tertiary blast outcomes, and to translate that knowledge to the design of PPE or find effective neuroprotective agents. This project includes a wide spectrum of analyses ranging from examining injury at the cellular and tissue level using preclinical and human cadaver models to validating the molecular findings with sophisticated computational models in order to fully understand the specific injury mechanisms associated with blast-related injuries. The experimental portion will include comprehensive histological assessments of brains collected from 12 swine and six cadaveric human

specimens that will be exposed to blast. This experimental effort will be supplemented by a computer modeling effort which will extend the results of the experimental tests to blast scenarios that are not easily obtained experimentally. During FY16, a detailed histological study of blast-exposed swine brains demonstrated the presence of damage to both axons and neuronal cell bodies using standard staining techniques. Specifically, animals exposed to open field blast demonstrated marked axonal changes in the cortex and cortical white matter tracts of the frontal lobes as measured with beta-amyloid precursor protein immunohistochemistry and changes in the number of astrocytes and microglia. In addition, the presence of Glial Fibrillary acidic protein (GFAP) was noted almost exclusively in the white matter tracts which may support an ongoing axonal injury. GFAP may be considered as one of the key serum markers of blast-induced changes due to the high astrocyte counts, close association of GFAP staining in the white matter tracts, and the increased GFAP levels within the serum of the animals exposed to blast. The team is currently completing the quantification of the immunohistochemistry from the posterior aspects of the brain that will offer insights into the extent of the injury in various lobes of the brain including the brainstem. To date, one cadaver has been tested and researchers are in the process of obtaining additional samples. In addition, the previously developed computer models of the swine and human brain are in the process of being validated against the acquired experimental data. Once these models are developed and validated, they can be used to develop more effective PPE in order to lessen the likelihood of blast-related injuries within the military population.



### **Multi-omics Analysis of Nutritional Countermeasures Used against TBI and Traumatic Stress in Rodent Models**

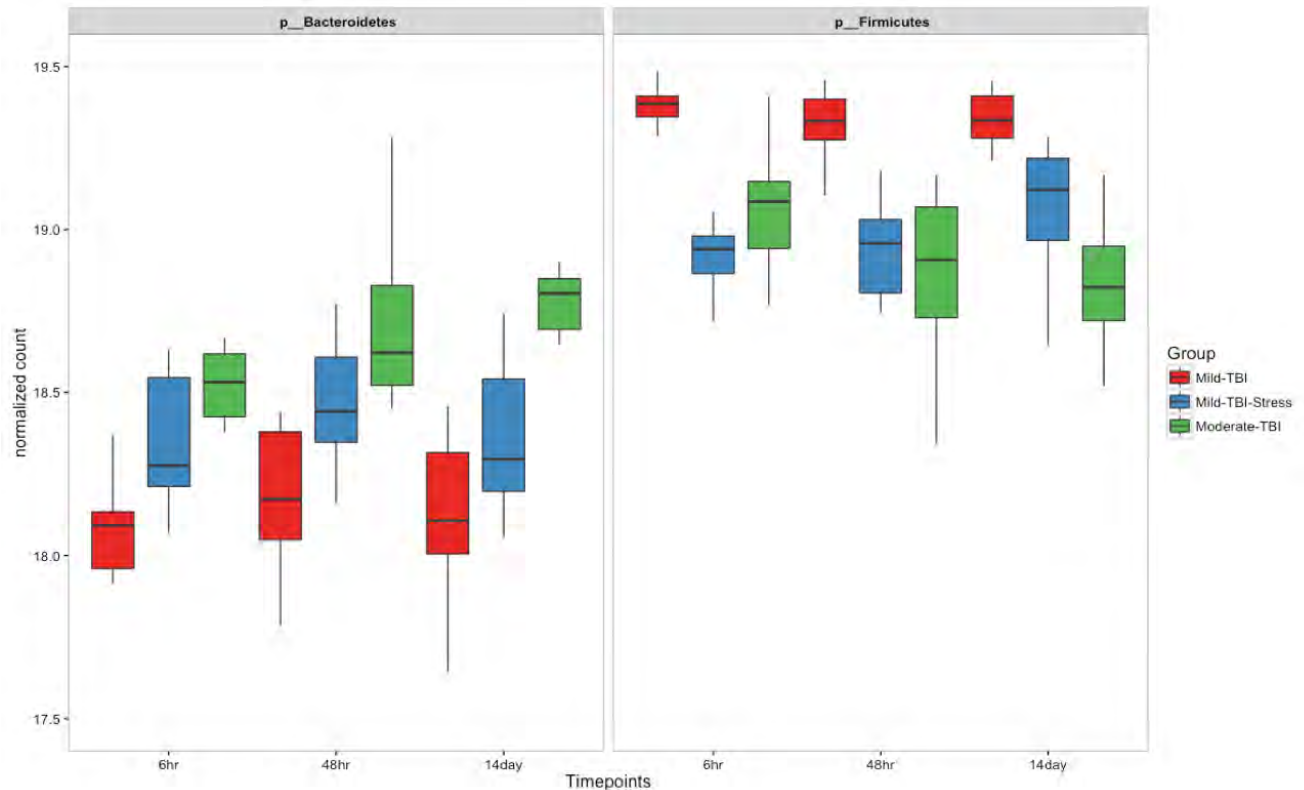
Researchers at the Integrative Systems Biology Program (US Army Center for Environmental Health Research (USACEHR)) are working with collaborators from the Military Nutrition Division (US Army Research Institute of Environmental Medicine (USARIEM)) and the Blast-Induced Neurotrauma Branch at WRAIR to evaluate injury-induced changes in rat models of TBI using multi-omics assays. The focus of this research is to study closed head TBI in the context of a single concussion and adding external stressors (e.g. immobilization), adding nutritional interventions, and defining the cell biology, neurology (motor, memory, and emotional damage), and RTD (recovery) questions. USARIEM researchers hypothesized that the ingestion of an anti-inflammatory dietary mix as post-injury treatment agents will decrease cognitive deficits and the extent of closed-head neurohistological traumatic injury in these rats. WRAIR researchers hypothesized that the unfavorable brain polyunsaturated fatty acids (PUFA) composition frequently seen in the typical Western diet (resulting from n-3 PUFA deficiency associated with the n-3/n-6 dietary imbalance) increases vulnerability to TBI-related disorders. Together the researchers predict that diets supplemented with n-3 PUFA will reduce this vulnerability when given prophylactically prior to the TBI and will enhance recovery when continued post-TBI or stress. Using laboratory rats maintained on specially formulated diets, WRAIR has explored this possibility employing established models of blast TBI and traumatic stress to ascertain whether vulnerability to TBI or stress is exacerbated by the n-3 PUFA-deficient diet. Researchers at USACEHR have been assaying the samples using several -omics platforms including messenger

ribonucleic acid (mRNA) complimentary deoxyribonucleic acid (cDNA) array, micro ribonucleic acid (miRNA) sequencing, liquid chromatography–mass spectrometry based metabolomic assays, and targeted proteomics to identify and validate potential surrogate markers from blood and neuronal tissues. USACEHR is also performing metagenomic assays to observe changes in microbiome and metabolite content in response to stressor exposure using these rodent models. The aim is to identify model-specific and cross-model conserved putative biomarkers after integrating multi-omics readouts. Preliminary data from USARIEM using rats exposed to mild or moderate TBI showed that exposure to acute immobilization stress significantly affected bacterial populations in the large intestines of rats exposed to mTBI (Figure 7-3). Current studies are assessing the pathophysiological responses associated with moderate TBI that are ameliorated by an anti-inflammatory diet, using this systems biology approach. Researchers at WRAIR are conducting parallel rodent experiments in which the influences of different n 3/6 ratio diets on responses to TBI and stress are being assessed. The researchers anticipate that as the evaluations of samples from this study progress, the molecular characteristics of these cohorts may provide insights into the interplay of nutritional status and trauma along with revealing potential benefits of dietary supplementation and providing additional opportunities for dietary supplementation in Service Members exposed to TBI.

### **Blast-induced Acceleration in a Shock Tube: Distinguishing Primary and Tertiary Blast Injury Mechanisms in Rat TBI**

Discerning biomechanical underpinnings is crucial for an understanding of the etiology and mitigation of blast-induced TBI. Scientists and engineers at WRAIR

**FIGURE 7-3:** Gut Microbiome Changes at Phyla level-TBI in a Rat Model



are teaming with world renowned blast physics experts in examining the interplay of BOP and accelerative forces using an ABS, which is capable of producing high fidelity IED-like blast waveforms in the laboratory. This undertaking involves understanding the role that parameters such as areal density (the mass of an object divided by its projected two dimensional area), play in the scaling of acceleration and displacement (e.g., blast throw) resulting from blast shock waves. Experiments to date on spheres of varied mass indicate that trajectories for similar sized objects overlay each other when scaled by areal density.<sup>33</sup> However, trajectories do not scale across a range of sphere sizes and the entire mode of blast-induced acceleration changes with sphere diameter. For larger spheres the initial diffraction-phase loading dominates, and motion starts with a brief ‘kickoff’ velocity followed by immediate deceleration with

the passage of the shock front. In contrast, for smaller diameter spheres acceleration was predominantly drag-dominated, with deceleration coinciding with the negative phase of the shock wave. The range of sphere sizes evaluated spanned the regime where acceleration was drag-dominated (for smaller spheres) to diffraction-dominated (for larger spheres) with a uniformly-applied shock wave profile having a strong decay with a six milliseconds positive phase duration. These characterizations are yielding great insight into scaling issues in laboratory experiments addressing human blast injuries as well as into the mechanisms that cause BOP TBI. By defining the scaled physical interactions of blast shock waves with test subjects, these findings when extended will provide valuable insights into biomechanical mechanisms underlying blast injuries in Service Members and associated mitigation measures.

### **UBB Models of TBI Caused by Hyper-Acceleration and Secondary Head Impact**

The vast majority of TBI suffered by Service Members is caused by blasts and these injuries are often inflicted upon occupants of vehicles targeted by IED. However, almost all of the animal research on blast TBI has concentrated on blast overpressure and has not taken into account the hyper-acceleration generated by UBB. With funding from the PH/TBIRP managed by CDMRP, an interdisciplinary team of researchers at the University of Maryland Schools of Engineering and Medicine will use their previously developed rodent model of blast TBI caused by hyper-acceleration generated by UBB to elucidate the pathophysiology of TBI caused by UBB-induced hyper-acceleration. This model will be used to better understand the forces responsible for TBI caused by UBB and to mitigate these forces through modifications to vehicle hull designs. This knowledge will help guide the design of future military vehicles, with the goal of mitigating brain injury and other forms of trauma caused by UBB. To date, the study team has established the minimum UBB-induced gravitational force that produces TBI and the maximum that is survivable and is now combining this injury with a secondary head impact to better model the injuries experienced by Service Members in the field. The team is also testing possible mitigation techniques to reduce the energy transferred from the blast to the animal. One promising technique is a thin walled aluminum tube which is coated in polyurea. This device was found to reduce the gravitational force from the blast acceleration resulting in increased survivability and reduced injuries. This research will provide the first direct insight into the pathophysiology of mild TBI caused by hyper-acceleration generated by UBB and will establish the first animal model of TBI caused by this form of acceleration plus secondary head impact. This work taken together with tests of different vehicle hull designs on

UBB-induced TBI will likely result in both engineering- and biomedical-based mitigations for TBI suffered by Service Members present within vehicles targeted by IEDs.

### **Mechanisms of Shock Wave Propagation to the Brain after Exposure to Blast**

The DMRDP managed by CDMRP funded the research at NMRC to study blast wave propagation through the body. The purpose of this study was to determine how a blast wave can transfer through the body and cause damage to the brain, despite helmet protection. This study used rats as the study population and tested against four hypotheses: (1) shock waves can enter the brain either directly via the skull or indirectly via the vascular system; (2) shock waves can enter the vascular system from any part of the body; (3) internal pressure can ameliorate propagation of the shock wave through tissues and blood vessels; and (4) pressure propagation through blood vessels results in cerebral hemorrhages. To accomplish this research, the rats were placed in a blast tube with either their head or tail towards the blast source to compare injuries to the brain. The rats are also provided with protection to their heads or bodies to simulate armor. The results of the study provided the following conclusions: (1) shock waves penetrate the skull and systemic circulation, and potentially they can interact and contribute to the resulting pressure in the brain; (2) whole body protection against blast does not protect against propagation of pressure in the brain, it changes but does not eliminate the presence of shock waves in systemic circulation; (3) contribution of indirect shock wave transmission to the brain depends on head and body shielding, shock waves can diffract and change direction; (4) head protection does not protect against shock wave entry into the brain; (5) wave propagation in vessels could have an impact on brain vasculature and could affect the blood-brain barrier (BBB) permeability by



damaging endothelial cells. Understanding the mechanisms whereby blast waves reach the brain, will facilitate development of better PPE to mitigate brain injury in the future.

## Protective Equipment

### Effects of Blast Injury on Hearing in a Screened Military Population

Exposure to hazardous intensity levels of combat noise, such as blast, may compromise a person's ability to detect and recognize sounds and communicate effectively. Previous studies have not examined the onset of hearing health outcomes following exposure to blast in a representative sample of deployed military personnel. In addition, definitive audiometric patterns of Service Members with blast-related injuries (BRIs) have not been adequately described in the literature. Researchers from NHRC analyzed data from the Blast-Related Auditory Injury Database. Subjects included only those with a qualified hearing test within a period of 12 months

prior to and following injury (n = 1,574). After adjustment for relevant covariates and potential confounders, those who sustained a blast injury had significantly higher odds of post-injury hearing loss, low frequency hearing loss, high frequency hearing loss, and significant threshold shift compared with a non-blast-injury (NBRI) group. An estimated 63 percent of risk for low frequency and high frequency hearing loss in these blast-injured, deployed military members could be attributed to the BRI event. Researchers also calculated median audiometric thresholds for the left and right ear at the test frequencies 500, 1000, 2000, 3000, 4000, and 6000 Hertz for audiograms prior to and following injury, and compared groups according to injury (BRI versus NBRI). Overall, median-threshold audiograms revealed hearing within normal limits (responses greater than 25 decibels Hearing Level) at all test frequencies for both ears. New-onset hearing loss primarily affected the frequency range of 4000–6000



Photo credit: Yuriy Dyachyshyn/AFP

Hertz, and hearing shifts were greater in the left ear. Post-injury low frequency pure-tone averages and high frequency pure-tone averages were significantly higher in those with a blast injury compared with the NBRI group for both ears ( $p < 0.001$  for all comparisons). On average, new-onset high frequency hearing loss was also accompanied by low frequency hearing loss. Additionally, when isolating infantry personnel, the blast-injured group had significantly higher pure-tone averages in both ears than the NBRI group.

Auditory health and readiness are critical components of situational awareness and QOL for the military and our combat Veterans. The results of NHRC's investigation about the hearing health status of deployed Service Members could provide decisive insight about operational readiness, injury prevention, and related medical problems. Continued surveillance of this BRI group may result in the emergence of a signature audiometric pattern for blast exposure in the theatre of war. Preliminary findings suggest there are greater hearing shifts in those with a blast injury than those with no blast injury, and further scrutiny may reveal unique patterns in subgroups of the population. It is imperative to continue to monitor the effects of blast injury on hearing outcomes, identify at-risk populations for early intervention and prevention, develop supportive policies and best practice guidelines, and allocate appropriate funds and resources.

### **Computational Model of the Eye for Primary and Secondary Blast Trauma**

Ocular trauma is one of the most common types of combat injuries resulting from the exposure of Service Members to IEDs. However, the injury mechanism associated with the primary blast wave remains mostly unknown. For example, the magnitude and character of the stresses and strains (e.g., shear, tension) in the tissues of the eye caused by the blast wave are

not well understood, nor are the factors that determine the distribution of the BOP to the eye. Moreover, the criteria for mechanical and functional damage to important ocular structures are unknown. Under the auspices of a grant funded by the Vision Research Program managed by CDMRP, the research team at the JHU Mechanical Engineering Department has developed a computational model of primary blast injury to the eye. The model includes fluid-structure calculation of the interaction of the blast wave with the facial features of a typical 21 year old male without eye-protection and with spectacles or goggles. The model also included a detailed model of a deformable eye with physiological representation of the main internal ocular structures of the eye, spatially varying thickness of the cornea-scleral shell, and nonlinear tissue properties. The model was applied to calculate the intraocular pressure and stress state of the eye-wall and internal ocular structure caused by different blast conditions. Researchers have found that the facial features have an important effect of amplifying the blast pressure loading on the eye for certain blast conditions.<sup>34</sup> Goggles were significantly better than spectacles at reducing the maximum pressure loading on the eye, but goggles trapped the high pressure blast wave in front of the eye for significantly longer duration than spectacles. The consequence of this prolonged exposure to a lower level pressure loading to the eye versus that incurred by the short duration pressure peak is unknown. The simulations also found the highest tensile and compressive stresses at the fovea and optic nerve head, which may be consistent with choroidal hemorrhaging, retinal detachment and damage, and optic nerve damage.<sup>35</sup> The distortional stresses were highest in the sclera at the attachment with the extra ocular tissues. The simulation outcomes were applied to three different injury models. Two of the models were developed for blunt impact injuries to the eye and the third was developed from in vitro experiment of blast loading to porcine

eyes. Different injury models produced widely different injury risk. This finding highlights the need for integrated modeling and experimental studies to evaluate mechanical and functional damage to the ocular structures caused by blast loading. Such an integrated study would provide specimen-specific correlation of the blast conditions, level of tissue-specific stress magnitude, and functional and/or mechanical damage. This model is expected to enable the development of improved protective devices for the eye and surrounding tissues. Enhanced protective devices have the potential to reduce long-term morbidity from ocular injuries for the Service Member.

### **Improvement and Extension of Auditory Hazard Models**

This study is performed by researchers at USAARL and funded by the DMRDP which is managed by CDMRP. The objective of this project is to fully document the effects of acoustic impulses on the middle ear and middle-ear muscle contractions (MEMC). This project will evaluate how the middle ear musculature reacts to warned and unwarned exposures to acoustic impulses, and if participants can be trained to react with this potentially protective reflex. This information is necessary for the development of damage risk criteria and health hazard assessment methods for exposure to high-level acoustic impulses such as experienced by users of military weapon systems and high-level impulsive noises such as from blasts. During FY16, the investigators completed the initial portion of the study by evaluating the rates of acoustic reflex prior to any training. In the upcoming year, investigators will examine if the MEMC reflex can be classically conditioned in a laboratory setting. Knowledge from this study could inform the development of training to boost the protective MEMC in Service Members.



Photo credit: SSG Jon Long/US Army

### **Ballistic and Blast Protection 2016 Research Goals**

The TRADOC Maneuver Center of Excellence (MCoE) is a participating partner in the Soldier Ballistic and Blast Protection Community of Practice established at the direction of the Commanding General, RDECOM after a series of meetings in 2010 and 2011. In addition to MCoE, participants include Natick Soldier Research and Development and Engineering Center (NSRDEC), ARL, TRADOC Army Capabilities Integration Center (ARCIC), USAMRMC, RDECOM, Program Executive Office (PEO) Soldier, National Ground Intelligence Center (NGIC), and the Office of Naval Research (ONR). The purpose of the Community of Practice has been to involve all parts of the PPE lifecycle (S&T, combat developers, and PEOs) to commit resources towards common goals. The output of this Community of Practice is the creation of research goals for soldier protection. The goals are aligned along four commodity areas of soldier protection: extremity, head, sensory, and torso. For 2016, the Community of Practice identified over 200 research gaps in soldier protection. The Community of Practice identified over 80 technical goals based on the research gaps and then consolidated these into 28 major goals. The goals were compared to the priorities expressed by TRADOC and PEO Soldier for the community, their potential to improve Soldier protection technology, and



their need for government S&T investment. The Community of Practice is using these goals as a roadmap for future technology development for soldier protection from ballistic and blast threats.

### **Polymer Coating for Protection against TBI**

The ONR supported efforts at Naval Surface Warfare Center, Carderock Division (NSWCCD), NRL and Naval Surface Warfare Center, Dahlgren Division (NSWCDD) to develop and optimize low-cost helmet coatings that exploit the shock and ballistic performance of highly rate-sensitive polymer coatings (HRSPC), developed under ONR S&T investments. HRSPC have been demonstrated to provide added protection against shock wave-induced mTBI, along with ballistic protection, without additional weight added to the helmet. Results were shared with NSRDEC. Earlier investigations by NSWCCD and NRL showed that HRSPC applied to an existing helmet could provide significant reductions in intracranial impulse during blast tests using full-scale instrumented head-neck manikin surrogates. However, the added coating resulted in a heavier helmet. New underweight helmets were fabricated from conventional Kevlar, Kevlar XP H170 and Tensylon fabric, which were coated with the selected HRSPC to the equivalent weight of a standard helmet, and tested for the ballistic requirements. Blast tests were performed at NSWCCD test pit and at Naval Surface Warfare Center, Indian Head Explosive Ordinance Disposal Technology Division using larger IEDs at a defined range of blast conditions. Blast pressures selected were based on likelihood of generating mTBI conditions using Bowen Blast Curves and findings from Army Research Office Multidisciplinary University Research Initiative (University of Pennsylvania, Columbia University, Duke University). Measurements on the test manikins included pressure, impulse, acceleration, and power intensity at different intracranial sites. Examination of different

coatings and thicknesses showed that certain thin coatings could reduce intracranial power intensity by 23 percent, but an even better result of 38 percent was realized when ballistic fabric material was coupled with the coating. These combinations met ballistic specifications. NRL developed hollow silicon carbide spheres that were embedded in the HRSPC applied to the helmets. These coatings provided improved performance for blast mitigation of tested Kevlar designs, reducing acceleration by 30-40 percent when compared to the standard Advanced Combat Helmet (ACH). Ballistic tests were done to enumerate different mechanisms of energy absorption/deflection at different temperatures and different coating glass transition temperatures. Hopkinson-bar tests were used to study various design parameters and to optimize performance, including: (1) effect of molecular weight and blending of the components of the polymer coating; (2) composition and layering variations of laminate coatings; and (3) substrate hardness and its coupling to the coating. NSWCDD conducted a series of blast attenuation tests on several Kevlar composites and HRSPC/composite combinations. Tests were done in a single stage gas gun with a shock tube to simulate low-amplitude planar blast waves at 0.5 – 2.5 bar. This blast range is required for studying material effectiveness for TBI mitigation. The planar blast waves induced one-dimensional strain in the target materials. HRSPC applied to the impact side of Kevlar composites can reduce output stress of Kevlar, thus mitigating TBI pressures.

Lightweight ACH and Enhanced Combat Helmet designs that reduce the possibility of mTBI results were verified against actual IEDs and close-in explosive tests using acceptable intracranial exposure levels, impulse, and acceleration criteria. The proposed polymer coated helmet exceeds military standards (MIL-STDs) ballistic requirements, while satisfying all other MIL-STDs. In addition, the coating, while enhancing the helmet performance for protection against mTBI, ballistic, and weight requirements, offers



Photo credit: Tracy McKithern/US Army

at the same time protection against sharp-edged flechette-type devices. Researchers at NSWCCD and ONR received the 2014 Vice Admiral Harold G. Bowen Award for Patented Inventions for their contributions to the patent “Armor Including a Strain Rate Hardening Elastomer.”

### **Assessment of the Effectiveness of Eyewear against Blast-induced Eye Injury**

Blast-induced ocular injuries were responsible for nearly 80 percent of all ocular injuries during OIF.<sup>36</sup> Ocular injuries from explosive devices, such as IEDs, can result from the interaction of a blast wave with the eye (primary blast ocular injury), penetrating trauma to the eye (secondary blast ocular injury), blunt trauma to the eye (tertiary blast ocular injury), and thermal burns (quaternary blast ocular injury).<sup>37</sup> In fact, exposures to IEDs were responsible for 51 percent of blast-related ocular injuries.<sup>36</sup> To prevent eye injury from shrapnel and other ballistic fragments during combat operations, Service Members are mandated to wear spectacles or goggles from the Authorized Protective Eyewear List.<sup>38</sup> Even though the use of protective eyewear reduced the incidence of ocular injury,<sup>39</sup> 8,323 such events were reported at MTFs in theater between 2005 and 2010.<sup>40</sup> An epidemiological study correlated the use of eyewear with a reduction in penetrating eye injuries (often associated with secondary blast ocular injury). However, no such correlation was reported for closed eye injury (associated with both primary and secondary modes of blast ocular injury).<sup>41</sup> This lack of correlation between the use of eyewear and closed eye injury may be attributed to the inability of the eyewear to protect the eye from a blast wave. In addition, various BOP studies ranging from 120 to 210 kilopascals have reported ocular injury in animals, such as a decrease in retinal ganglion cell response in mice,<sup>42</sup> corneal edema and photoreceptor cell loss in mice,<sup>43</sup> and damage to cells of the optic nerves

in rats.<sup>44</sup> Therefore, to better characterize the pressure loading to the eye due to blast wave exposure and the benefits of protective gear, in collaboration with the USAARL, the BHSAI, a subordinate organization of the Telemedicine and Advanced Technology Research Center (TATRC) of the USAMRMC, Fort Detrick, Maryland, investigated how eyewear interacts with BOP.

To this end, in collaboration with USAARL, BHSAI developed three-dimensional FEMs of a headform fitted with an ACH and Revision Sawfly Tactical spectacles, as well as a FEM of a shock tube.<sup>45</sup> BHSAI researchers performed computer simulations with the head facing the blast wave (0°) and with the head rotated at 60° and 90° relative to the direction of the propagation of the blast wave, with and without spectacles and then validated the model by comparing the results with experimental data. At 0° orientation, the maximum pressure on the left eye without spectacles was 2.75 times the incident blast pressure, and with spectacles it was 1.75 times the incident blast pressure (Figure 7-4).<sup>45</sup> This was in agreement with experimental observations (2.76 and 1.93, respectively). Without spectacles, at 0° orientation, the blast wave loading to the eye was primarily a combination of reflected pressures from the eye, forehead, and cheek. At 60° and 90° orientations, in agreement with experimental data, BHSAI researchers observed an intense secondary loading on the left eye. With spectacles, the blast wave reached the eye through the gap between the spectacles and the face and was amplified due to reflections from the inside of the spectacles. However, the spectacles prevented secondary loading to the left eye at 60° and 90° orientations. From the computer simulations, BHSAI quantitatively characterized the protective effectiveness of spectacles in reducing the blast pressure to the eye and determined how the blast wave loading mechanisms to the eye were modified by the eyewear.<sup>45</sup>



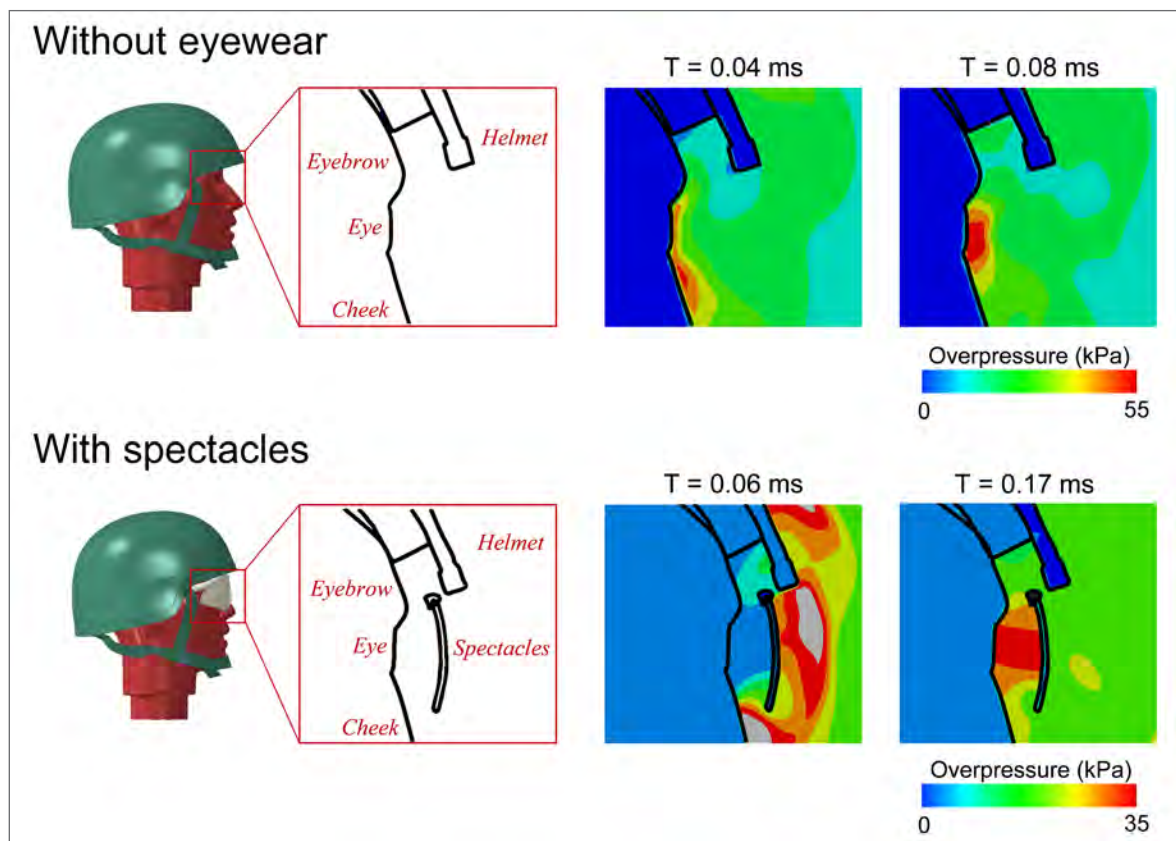
The results from the simulations and USAARL experiments demonstrated that the use of spectacles reduced the intensity of BOP on the eye during a head-on blast wave exposure. However, at other orientations, the protective effectiveness of spectacles in reducing the blast pressure to the eye is significantly diminished because the blast wave enters into the confined space between the eyewear and the eye through the gap between the spectacles and the face and is amplified. The quantification and improved understanding of the protective effectiveness of spectacles against blast wave exposure can help guide the design of future eye-protective gear.

### Wearable Noise Dosimetry for Tactical Environments

In theater, exposure to hazardous noise levels is a known threat to Service Members; however, it is difficult to obtain individualized

characterizations of such exposure in tactical environments. To address the lack of data, the Bioengineering Systems and Technologies Group at the MIT Lincoln Laboratory successfully fielded prototype helmet-mounted and modified commercial off-the-shelf acoustic sensors in August 2013 through collaborations with the Marine Expeditionary Rifle Squad and USARIEM. The sensor was designed specifically to collect high decibel-level noise and was hardened for tactical data collection during US Marine Corps dismounted operations out of Patrol Base Boldak, Afghanistan. To maintain operational security, speech content was removed from the recorded data, while the relevant noise exposure information was preserved. The 274 hours of combat audio data collected in Afghanistan by 19 Marine volunteers captured their exposure to vehicle noise and weapons fire. Analysis of the data by MIT Lincoln

**FIGURE 7-4:** Comparison of Blast-wave Induced Pressure Loading to the Eye With and Without Spectacles



Laboratory in FY14 revealed that the majority of the Marine volunteers were exposed to noise conditions exceeding 85 A-weighted decibels, the safety threshold set by the National Institute for Occupational Safety and Health, over the course of a two-day collection period. In addition, several Marines were exposed to noise conditions that greatly exceeded the 500 auditory risk unit (ARU) impulse noise limit set by MIL-STD 1474E.<sup>18</sup> During one firefight that occurred during the data collection period, one Marine's exposure even exceeded 2500 ARUs. In FY15, development started on a second-generation prototype wearable device funded by the Marine Expeditionary Rifle Squad and the US Army NSRDEC. The new device incorporates improvements such as a higher sampling rate, expanded dynamic range, onboard processing to provide real-time exposure metrics, global position system, and wireless connectivity capabilities. Continued development and validation testing of the second-generation prototype began in March 2016. The ONR has also taken the lead to field the device in order to support an existing US Marine Corps/Navy study of hearing injury sustained during Marine rifle training exercises. The ongoing work to collect individualized exposure data will help to more accurately quantify its complex relationship with hearing injury. Results will ultimately enable the development of more accurate exposure limits and hearing protection criteria for combat environments, which could help reduce the risk of hearing loss and increase hearing protection usage compliance.

### **Novel Dendrimers for Antimicrobial Textile Finish**

Wound infection following blast-related injuries continues to be a significant source of morbidity and mortality in the modern era of military healthcare. Approximately a quarter of combat wounds become infected, having a significant impact on patient outcomes and healthcare costs. Therefore, there is a need to identify a light-weight, durable, antimicrobial finish for integration into textiles to control

the transmission of pathogenic bacteria and minimize infection in military medical shelters and field hospitals. An important component in the overall strategy for improving soldier performance and developing Smart Textiles is that the antimicrobial finishes should not cause the degradation of other properties of the fabric (e.g., porosity or mechanical properties). Research supported by the DoD SBIR Program topic, "Antimicrobial Textiles," will focus on developing and optimizing catalytic antimicrobial systems for direct integration into fabric for clothing, shelters, and wound dressings. As part of a previously completed Phase I SBIR project titled "Novel Dendrimers for Antimicrobial Textile Finish," Physical Sciences, Inc. (PSI) successfully synthesized and chemically coupled a novel antimicrobial dendrimer to cotton fabric. In the follow-on Phase II, PSI will continue to develop this antimicrobial compound by improving protocols to scale up the synthesis of the dendrimer, creating a process to attach the dendrimer to multiple fabric types, and performing comprehensive characterization of the fabric properties to ensure both safety and durability of the compound. The resulting technology will be easily integrated into fabric weaving and manufacturing and it will be scalable to a high through-put process, allowing large volumes of fabrics to be treated. This technology will have both DoD and civilian applications, including the inclusion in antimicrobial textiles, anti-infective wound dressings, medical devices, and hospital textiles, bedding, and wipes. Following the completion of Phase II of this project, PSI will direct their focus towards developing a comprehensive program for commercialization of this product to transition it from the laboratory to use within the field or hospital setting.

### **Head Protection**

Product Manager Soldier Protective Equipment within the US Army PEO Soldier has developed the Integrated Head Protection System (IHPS), a subsystem

of the SPS for head protection, with an integrated maxillofacial protection subsystem comprised of a removable mandible and visor (Figures 7-5 to 7-7). The IHPS maxillofacial protection subsystem protects mounted Service Members, such as turret gunners, from common blast fragments. The IHPS also leverages the lessons learned from research completed in conjunction with the University of Nebraska at Lincoln to effectively mitigate BOP events under operationally relevant threat scenarios. The IHPS provides head protection, to include face, from blast wave and fragmentation from blast and ballistic threats and therefore will provide superior protection from a wider variety of explosive threats than any previously issued standard combat helmet. Milestone C authority approved the IHPS for low-rate production in the fourth quarter of FY16.

#### **Use of Rigid Eye Shields at the Point of Injury**

As part of an on-going effort to educate and improve compliance, VCE developed an instructional video on the use of rigid eye shields, “Shields Save Sight.” This video<sup>46</sup> placed third<sup>47</sup> in the “Internal and Public

Information” category at the Defense Media Activity Department of Defense Visual Information Production competition<sup>48</sup> - the highest level of competition for video production within the DoD. The outreach was extended from military medical providers to civilian trauma providers and included



**FIGURE 7-5:** Modular Helmet- primarily worn by all dismounted Soldiers in a tactical environment. This configuration provides limited rifle protection. (Photo courtesy of Brandon Motte.)



**FIGURE 7-6:** Modular Helmet with attached maxillo-facial protection (mandible and face shield) worn by Soldiers who man machineguns (turrets) exposed to kinetic and fragmentation threats. The turret configuration may also include the Modular Ballistic Appliance. (Photo courtesy of Brandon Motte.)



**FIGURE 7-7:** Modular Helmet with Modular Ballistic Appliance. Worn by dismounted Service Members for short durations during assault to objective type scenarios. This configuration provides increased rifle protection over the modular helmet alone. (Photo courtesy of Brandon Motte.)



target audiences of medical providers of all levels, Service Members, and members of the civilian trauma community. The video has been incorporated into the Committee on Tactical Combat Casualty Care All Combatants curriculum as well as the National Association of Emergency Medical Technicians pre-hospital care curriculum.<sup>49</sup> In addition to publicizing the instructional video, VCE continued to emphasize the need for rigid eye shields at the point of injury by presenting at the Eagle Creek breakout/pre-meeting of the 2016 A Gathering of Eagles Annual Scientific Symposium, the annual meeting of the Directors of State and Metropolitan Emergency Medical Services Systems.<sup>50</sup> Throughout the presentation, VCE emphasized that there is currently no national requirement for civilian ambulances and emergency vehicles to stock or carry rigid eye shields, resulting in a lack of ability to properly mitigate eye injuries at the point of injury. Primary examples of the impact of this gap included the Boston Marathon blast and the West, Texas explosion, both of which created ocular injuries in numbers similar to those seen in military combat. Despite a 12-14 percent rate of eye injury, only one shield was placed. As a result of the presentation, national ambulance stockage lists and recommendations will soon be changed to include rigid eye shields.

## Vehicles

### **Product Manager Heavy Tactical Vehicles Armor Kit Production**

During FY16, the Product Manager Heavy Tactical Vehicles (PdM HTV), Project Manager Transportation Systems of the US Army's Program Executive Office Combat Support and Combat Service Support continued production of armor kits for its fleet of tactical trucks. The contract with Fidelity Technologies Corporation (Reading, Pennsylvania) is working through its third of four years with over 1900 kits produced. PdM HTV, located at the Tank Automotive Command in Warren Michigan, manages a fleet of trucks including the



**FIGURE 7-8:** HEMTT Armored Cab

Heavy Expanded Mobility Tactical Truck (HEMTT) (Figure 7-8), Palletized Load System, and Line Haul tractors. The Heavy fleet plays a large part of Product Manager Transportation Systems' role in support of the Soldier and represents a significant capability for the Nation by enabling the Army's sustainment of joint force's operations. These systems ensure Soldiers have the required supplies and equipment to enable mission accomplishment. The US Army has made significant investments over the recent conflict to modernize and protect its wheeled vehicles. To maintain those gains and US force's overmatch against adversaries requires sustained investment. One of those investments is protecting the Service Member and armoring the fleet. The PdM HTV team and partners have been able to ensure the production of armor kits during current times of world instability and fiscal uncertainty. The production of these armor kits supports the Service Member whenever and wherever needed around the world. The armor kit production also contributes towards the Army's 2014 Tactical Wheeled Vehicle Strategy objective.

### **Casualty Status and Injury Profile of Mounted Service Members from a Select Group of Combat Events**

Armored vehicles were used extensively in both OIF and OEF by the US Military. Military vehicles, including armored vehicles,

are often the target of buried explosive devices, roadside bombs, and direct-fire attacks. On some occasions, these events can cause catastrophic damage to a targeted vehicle. Because of the constant push for increased preventive equipment and measures related to occupant safety, it is important to understand how or if there is a relationship between a vehicle with catastrophic damage and the casualty status and injury profile of the occupants. NHRC and JTAIC partners, using the JTAPIC database, examined a group of vehicles with catastrophic damage along with the casualty status of the occupants and their Abbreviated Injury Scale (AIS) coded injuries. Casualties, including WIA and killed in action (KIA), were described with frequencies and proportions. For WIA, severity of injury was described using frequency and proportions for each of the nine AIS body regions and crew positions. Using the Barell matrix, injury types were also examined by crew position. Lastly, WIA injury severity and KIA frequency were examined by event. A total of 25 like-vehicle events meeting the criteria for having a catastrophic level of damage were selected for study. Sixty percent (15/25) of the events had at least one WIA or KIA, 48 percent (12/25) of these events had at least one WIA, and 32 percent (8/25) of the events had only one WIA. Only 28 percent (7/25) of the events had at least one KIA, with 12 percent (3/25) having only one KIA. There were no WIAs with injuries exceeding an AIS 3 in severity, and 24 percent of the events had no WIAs with injuries exceeding an AIS 2 in severity. Drivers received the highest proportion of total coded injuries at 37 percent (67/181), but the highest proportion of WIAs were in a gunner/vehicle commander (VC) position (33 percent; 9/27). Lower extremity injuries accounted for the highest proportion of injuries experienced by WIAs and accounted for the highest proportion of coded injuries overall. Fractures and superficial/contusion injuries were the dominant injury types, with drivers having the highest proportion of

fractures, and gunner/VC positions having the highest proportion of superficial/contusion-type injuries. Only four events accounted for 63 percent (114/181) of the coded injuries and 76 percent (13/17) had AIS 3 injuries. One event accounted for 38 percent of all KIAs (5/13) and had no WIAs. In summary, the catastrophic damage to a vehicle does not necessarily directly relate to the outcomes experienced by the crew. In no case did a WIA injury severity exceed an AIS of 3, and 32 percent of the events had only WIAs. Vehicles with catastrophic damage retain the capacity to protect those in the crew compartment.

### **Enhanced Underbody and Crew Protection for the M1A2 SEPv3 Abrams Tank**

In addition to armor protection upgrades to the Abrams Tank, the Next Evolution Armor (NEA) development effort also addressed both weight reduction and crew protection improvements for UBB. Weight reduction was accomplished through a redesign of the existing Aluminum UBB kit that resulted in a thinner, lighter-weight Steel UBB kit which provided equivalent protection, improved ground clearance and mobility as well as simplified kit installation. Crew protection was significantly improved through incorporation of a mixture of stiffening the basket structure and reducing impulse/arresting secondary projectiles. Specifically, this was accomplished through the use of blast mitigating seats and footrests/blast mats, redesigned turret basket support posts, incorporation of expanded platform stiffeners, installation of a crushable mount for the hydraulic manifold and energy absorbing under-basket stanchions and redesign/strengthening of the access panel, hinges and locking mechanism. NEA UBB Improvements successfully completed UBB Testing using both legacy (Comer) and Engineered Roadbed soils, resulting in drastic improvement for the Loader and overall reduced severity of injury to the rest of the crew. All of these enhancements will be incorporated into the M1A2 SEPv3 Abrams Tank (Figure 7-9)



**FIGURE 7-9:** M1A2 SEPv3 Abrams Tank

scheduled to enter production on FY17 and will reduce casualties to the Abrams Tank System crew by providing blast mitigating and energy absorbing systems at the lowest possible overall system weight.

### **Product Manager Future Fighting Vehicles UBB Mitigation Programs**

Product Manager Future Fighting Vehicle, part of the Program Executive Office Ground Combat Systems (PEO GCS) in Warren, Michigan, has challenged its contractors on a S&T contract to develop designs for mitigation of injuries resulting from increasingly larger blasts. Researchers have found that by implementing: 1) engineered joints that ensure one weld is in tension and one in compression during blast deformation; 2) automated welding such as friction-stir welding and High Energy Buried Arc welding; and 3) innovative joining techniques like explosively-bonding dissimilar metals; hull ruptures have been eliminated for the same size blasts that, just a few years ago, would have caused catastrophic failures and hull breaches resulting in Service Member injury and death. The utility of these improvements have been demonstrated by multiple tests conducted at APG, Maryland, as

well as contractor facilities. Further, third-party modeling and analyses have verified that these improvements can be successfully used in future combat vehicle designs. Tests conducted by Army Research Laboratories Weapons Materials Research Directorate at APG, Maryland, and partially funded by Future Fighting Vehicles, have demonstrated the successful integration of the TenCate Active Blast Defense System (ABDS) on a notional ballistic hull and turret. The ABDS automatically senses an UBB and then applies a counter force to hold the vehicle down. In comparison tests conducted with and without the system, a 78 percent decrease in Service Member injuries due to slam down was observed by employing this active blast technology. Ultimately, incorporating advanced welding techniques and active blast technology into future combat vehicles will create safer vehicles, reducing injury and death of Service Members.

### **Modeling the Effects of Boots on Leg Injury Mitigation in UBB Events**

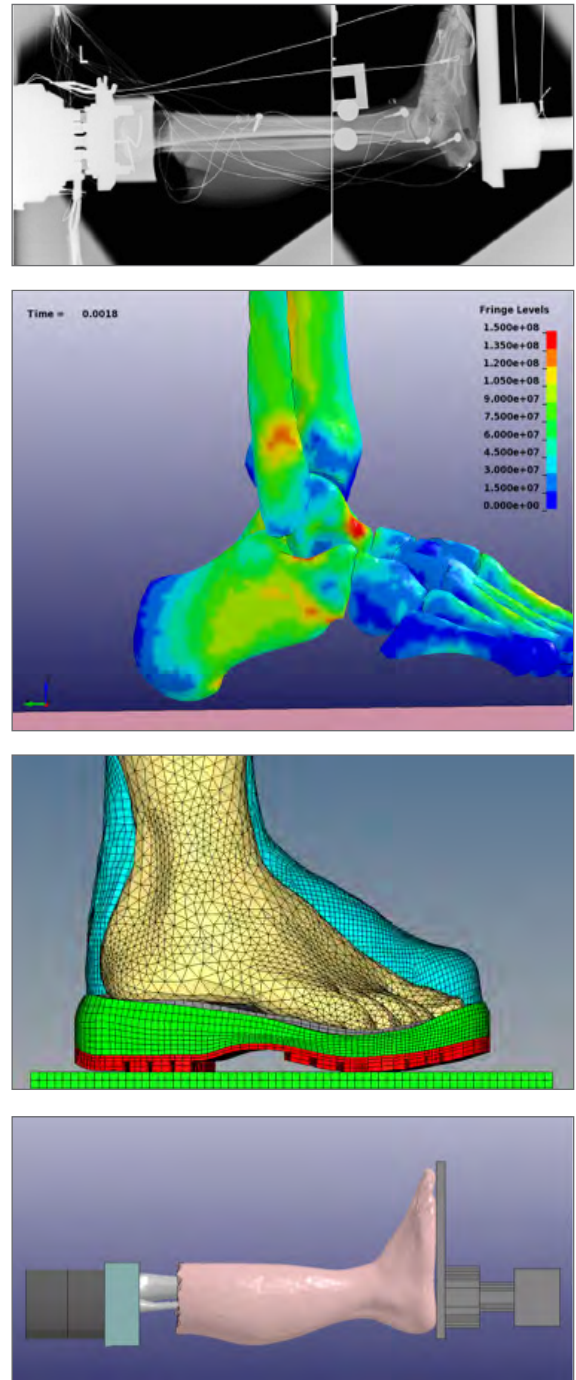
A FEM of the human lower leg was developed by USAARL from Computed Tomography (CT) data, and it was used to simulate



the response of the lower extremities to representative UBB exposures. The model was validated against available experimental data using postmortem human subjects. Simulations were run for both booted and unbooted conditions to assess the efficacy of boots to mitigate forces being transmitted through the floor into the lower leg, and to help quantify the associated risk of injuries to the Service Member. Simulations performed at varying levels of impact, mass, and velocity showed reductions of 34-40 percent in peak forces transmitted to the tibia. A validated FEM can be used to assess Service Member response to potentially harmful events, such as blast and ballistic loading. The lower leg model being described here has been used to evaluate the protective effects of boots, and can also help design and assess the performance of future improvements to PPE and other protective technologies (Figure 7-10). This can include both Service Member-borne and vehicle-borne systems.

### Dual Stage Energy Absorbing Mechanism for Vehicle Occupant Protection

In FY16, the RDECOM, ARL successfully demonstrated a dual stage energy absorbing mechanism that provided extra protection for vehicle occupants from an UBB. The design utilizes a novel shock absorbing floor and seat mechanism to mitigate energy and force transmission to mounted Service Members. The protection scheme was integrated into a 30 ton surrogate ground vehicle structure, and tested under elevated threat conditions (5X). Live-fire test results proved the concept highly effective at reducing injury to the lower legs and spinal column of seated occupants at a high level of blast threat. The results confirm performance predictions obtained through computational modeling and simulated blast testing, in a controlled laboratory environment. Findings can be applied to enhance vehicle protection and reduce probability of injury during UBB events.



**FIGURE 7-10:** The figures above represent experiments and numerical analysis to study how blast forces are transferred to the lower leg of a Soldier seated in a vehicle subject to blast loading. The numerical analysis enables an understanding of how stresses are transmitted through the skeletal structure, and how they can be mitigated with protective equipment.

### **Processing of Thousands of Incidents and Injuries into the Combat Incident Database**

In 2016, the Combat Incident Analysis Division (CIAD) at the NGIC input over 7,500 incidents and 6,700 persons into the Combat Incident Database (CIDB). This database enables CIAD analysts to recommend measures to mitigate enemy weapon effects against US personnel and equipment. Furthermore, the analysis of data within the CIDB provides senior policy makers and the acquisition community information needed to validate modifications and upgrades to equipment and protection systems, as well as afford theater commanders and deploying unit's feedback to modify US Army tactics. As the Army searches for ways to mitigate attacks against US personnel, and reduce casualties, it is vital that the CIDB is based on a solid foundation of data. Over the past year, the legacy effort which includes the Dismounted Incident Analysis Team at Fort Benning, Georgia and CIAD analysts at NGIC have updated over 2,500 incidents and 5,100 persons from 2003, 2004, and 2007. Additionally, while going through legacy records, CIAD discovered damage to types of vehicles that were previously not thought to have sustained combat damage. This updated data will ensure that RFI responses are as accurate as possible and will lead to a further reduction of injuries to US personnel. Vehicle programs such as the Stryker, Bradley, and Abrams have all benefited from this effort which will enable them to make more informed decisions on critical and costly upgrades to their systems.

### **Affordable Protection from Objective Threats Army/Manufacturing Technology (ManTech) Program (Vehicle Underbody)**

The RDECOM, ARL in collaboration with Israel under the US-Israel Armored Vehicle Underbody Blast Project Agreement (PA-A-14-0001); DARPA; RDECOM, TRADOC MCoE, the PEO GCS Future Fighting Vehicles

program; Alloy Technology Innovations; Corvid; Alcoa, BAE Systems; and TenCate; is executing an Affordable Protection from Objective Threats (Figure 7-11) Army Manufacturing Technology (ManTech) Program developing manufacturing processes required to produce aluminum hulls capable of withstanding very large Net Explosive Weight UBB threats. The manufacturing processes investigated include forging, forming, and advanced welding technologies. Lower hulls have been successfully fabricated using each of these manufacturing paths, and live-fire blast tested on a massive test fixture. One forged hull and one formed hull have been integrated into ballistic hull and turret (BH&T) assemblies. The BH&T's have been outfitted with energy absorbing seats and floors. The forged BH&T was tested against a very large underbody charge, which resulted in several ATDs registering injury. The described BH&T was reset with the same seats and floor, and an ABDS. The BH&T was re-tested at the same very large underbody charge level, and with the ABDS, no ATDs registered any injury. Vehicles equipped with demonstrated technologies can withstand greater blast impacts than current systems with significantly less blast effects to vehicle occupants. These findings demonstrate force protection against objective threats to provide Army leadership with the cost and weight needed while achieving and informing requirements.

### **Program Area: Acute Treatment**

Research in acute treatment is intended to improve survivability and mitigate long-term disability for Service Members with the full spectrum of injuries following blast events. Collaborations between DoD and partners in the US FDA, academia, and the private sector are investigating new diagnostic tools, therapies for TBI, hemorrhage control devices, strategies to mitigate wound infection, and interventions for facial, auditory, and visual injuries. This section



**FIGURE 7-11:** Affordable Protection from Objective Threats – Aluminum Underbody Efforts

demonstrates how the research community is employing novel neuroimaging techniques, evaluating clinical data, and experimenting in the laboratory to address the spectrum of blast injuries. The combined efforts of researchers in this area will lead to a greater understanding of the capabilities and limitations of current technologies, new tools and validated methods for injury mitigation in the prehospital setting, and improved diagnostics and clinical guidelines for the acute treatment of blast injuries.

### Diagnostics and Biomarkers

#### **Assessing Quantitative Changes in Intrinsic Thalamic Networks in Blast and Non-blast mTBI: Implications for Mechanisms of Injury**

Researchers from NICoE investigating post-TBI biomarkers determined that blast and non-blast mTBI differ in the mechanism of injury, as seen by changes in thalamic network architecture. A significant number of network connections in the brain converge in the thalamus, which

suggests this region could be especially sensitive to posttraumatic changes in the brain. This study identified biomarkers of injury following mTBI, with a further comparison of the impact of blast or non-blast mechanisms of injury. Participants included 287 individuals that were separated into one of three groups: mTBI blast (n = 186), mTBI non-blast (n = 80) and uninjured controls (n = 21). Assignment to the blast group occurred if the blast injury resulted from primary, secondary, tertiary or quaternary mechanisms. Assignment to the non-blast group occurred if the injury occurred via blunt force trauma, such as falls, sports, or motor vehicle accidents. Self-report behavioral measures, consisting of the Neurobehavioral Symptom Inventory, Posttraumatic Stress Disorder Checklist-Civilian, Combat Exposure Scale and the 36-item Short Form Health Survey (SF36), were collected (Table 7-1). MRI data were collected using a task-free scan of six minutes duration. The results of this study showed that the blast mTBI group has significant



**TABLE 7-1:** Self-report Data for Controls, Blast mTBI Subject and Non-blast mTBI Subjects.\*

Measure	Subject Group	# of subjects who completed measure	% of subjects who completed measure	Mean	Standard Deviation
PTSD Checklist Civilian version – Sum	Controls	19	91%	18.842	3.304
	Blast mTBI	165	89%	52.782	17.946
	Non-blast mTBI	68	85%	48.600	21.217
Combat Exposure Score - Total Score	Controls	19	91%	2.737	5.496
	Blast mTBI	163	88%	27.634	7.763
	Non-blast mTBI	67	84%	18.000	12.91
Neurobehavioral Symptom Inventory - Total Score	Controls	21	100%	2.762	4.312
	Blast mTBI	186	100%	36.317	19.378
	Non-blast mTBI	79	99%	33.861	21.504
SF-36 - Physical Functioning	Controls	20	95%	78.810	25.194
	Blast mTBI	186	100%	50.350	26.998
	Non-blast mTBI	80	100%	49.063	27.606
SF-36 - Role limitations due to physical health problems	Controls	20	95%	83.333	35.649
	Blast mTBI	186	100%	22.177	34.905
	Non-blast mTBI	80	100%	30.313	39.317
SF-36 - Role limitations due to emotional problems	Controls	20	95%	90.476	30.079
	Blast mTBI	186	100%	33.512	42.799
	Non-blast mTBI	80	100%	39.999	44.184
SF-36 - Energy/fatigue	Controls	20	95%	69.524	20.670
	Blast mTBI	186	100%	25.952	19.735
	Non-blast mTBI	80	100%	27.938	24.634
SF-36 - Emotional well being	Controls	20	95%	83.619	20.353
	Blast mTBI	186	100%	43.742	25.156
	Non-blast mTBI	80	100%	47.650	29.319
SF-36 - Social Functioning	Controls	20	95%	86.905	25.148
	Blast mTBI	186	100%	42.003	29.306
	Non-blast mTBI	80	100%	45.469	31.899
SF-36 - Pain	Controls	20	95%	85.000	25.409
	Blast mTBI	186	100%	44.207	26.058
	Non-blast mTBI	80	100%	45.313	27.791
SF-36 - General Health	Controls	20	95%	81.195	24.078
	Blast mTBI	186	100%	43.763	25.296
	Non-blast mTBI	80	100%	46.250	27.427

\* from Brain Connectivity 6:5 389-402 (2016) used with permission from the authors.<sup>40</sup>

hyper-connectivity in the thalamus, when compared to controls and non-blast participants.<sup>51</sup> However, after controlling for the incidence of posttraumatic stress, the blast mTBI group was no longer different from the control group, but the non-blast mTBI group showed significant hypo-connectivity. These architectural differences in the thalamic networks suggest the potential for both differing mechanisms of injury, as well as the potential for images collected from this region of the brain to be used as a biomarker of injury.

#### **Identification of Biomarkers of Heterotopic Ossification Following Extremity Blast Amputation: Animal Model Correlation with Human Disease**

Heterotopic ossification (HO) is an ongoing issue for wounded Service Members, particularly after blast injury. Complications related to HO in blast amputation residual limbs include pain, overlying skin and muscle breakdown, poor fitting and functioning of prosthetic limbs, reoperation for amputation revision, and impaired limb function that delays rehabilitation. Current treatments are poor, and limited to mitigation rather than prevention. Furthermore, removal of heterotopic bone after it has formed can be difficult; this frequently requires resection of substantial amounts of soft tissue and risks injury to adjacent neurovascular structures that are often intimately associated with the ectopic bone. It is preferable to address the issue of HO before it begins. Developing a rat model to better characterize gene and protein level expression is critical to the identification and treatment of HO in wounded Service Members. To address this need, researchers at USUHS have developed a survival animal model for HO after extremity blast amputation in the Sprague Dawley rat subjected to a controlled explosion that closely resembles injuries observed in Service Members. The model has a high incidence (~90 percent) of ectopic bone formation in the amputation site with reliable animal survival following the blast.<sup>52, 53</sup> Controlled study of this injury

holds promise for development of effective interventions to prevent complications related to HO in the residual limb for survivors of blast type amputations. To date, all hind-limb blast amputation procedures on 75 animals have been completed, as well as related scheduled biopsies. The harvested specimens are currently undergoing ribonucleic acid (RNA) profiling using an Osteogenesis pathway specific RT<sup>2</sup> Polymerase Chain Reaction array (SABiosciences) to determine the correlation of osteogenic marker expression between the treatment groups. Many of the genes determined from these analyses still need further molecular and cellular biology investigation to better understand their function.

Correlation of animal and human HO findings will allow identification of common biomarkers that are present early in the process and are predictive of HO formation in wounded Service Members at greatest risk. Biomarker identification of Service Members likely to develop HO, as well as potential prevention of HO is needed to offer amputation survivors the best possible QOL. In the future high-risk individuals will ultimately be able to enroll in a clinical trial of therapeutic interventions known to effectively prevent HO in the civilian setting. Human tissue sample collection from wounded Service Members treated at WRNMMC will start as soon as IRB approval is received. This research is being conducted at USUHS and is funded by the Peer Reviewed Orthopedic Research Program (PRORP) of the CDMRP.

#### **A Panel of Serum miRNA Biomarkers for the Diagnosis of Severe to mTBI in Humans**

Department of Pathology at USUHS is active in TBI research and was awarded a grant in 2010 from the DMRDP managed by CDMRP to establish a miRNA based biomarker for TBI. TBI is a problem with epidemic magnitude involving Service Members, civilians, and professional athletes. MTBI, more commonly referred to as a concussion, accounts for

more than 75 percent of the total reported TBI cases in the US Armed Forces. These mild injuries are often difficult to diagnose because of the absence of clear clinical symptoms and lack of sensitive diagnostic methods. Studies conducted within the Department of Pathology laboratory at USUHS have identified novel miRNA based biomarkers to diagnose mTBI. MiRNAs are small non-coding RNAs present inside a living cell which play key roles in the regulation of gene expression. In a recently published article in *Scientific Reports*, the collaborative research team identified a panel of miRNAs which show promise in detecting mild to severe TBI.<sup>54</sup> The research team investigated the presence of miRNAs in the blood samples from patients who suffered from an acute mild to severe TBI and compared these results with blood from healthy volunteers. A panel of 10 miRNAs was identified that were present only in the serum of mild to severe TBI groups and absent in healthy individuals and the trauma control patients. Four out of the 10 miRNAs were found to be present at higher concentration in the cerebrospinal fluid (CSF) in TBI patients in comparison to the controls. A patent application (Application no: PCT/US2015/036925) has been filed for this discovery. Another article accepted for publication in the journal *Brain Injury* describes the kinetics of miRNA expression changes in the brain after TBI and their potential molecular targets.<sup>55</sup> Previous work from the same laboratory identified a miRNA biomarker, let-7i, for blast induced mTBI.<sup>56,57</sup> MiR-let-7i, reported in this study has been included in a recently initiated (2016) clinical trial at the University of Vienna, Austria (<https://clinicaltrials.gov/ct2/show/NCT02639923>), to assess its potential to diagnose acute mTBI. These studies lay the foundation for the development of novel miRNA based blood diagnostic testing for TBI. These findings have the potential to improve the diagnosis of mild to severe TBI using a non-invasive biomarker to determine the extent of injury.

The ability to more accurately diagnose TBI may critically impact the medical care and safe RTD status of future Service Members with the goal of decreasing the long-term impact and complications of TBI.

### **Non-Invasive Immune Monitoring to Improve Outcomes in Composite Tissue Transplantation**

Combat related amputations have led to greater than 1100 amputations from the Afghanistan and Iraq campaigns with facial injury occurring in one third of combat casualties. Composite tissue allograft (CTA) transplantation provides a unique opportunity to treat combat wounded, improve QOL, and facilitate the return to active duty and occupation. Diagnosis of acute rejection (AR) remains dependent on non-specific clinical and pathological evidence. Therefore, novel concepts and innovative technologies are needed to non-invasively monitor AR that could be translated to long-term monitoring of chronic graft vasculopathy. Researchers at WRNMMC are actively studying non-invasive mechanisms for monitoring and recognizing AR following CTA transplantation. CTA transplants occur subsequent to disabling combat injuries involving hand, forearm, and craniofacial structures. Eighty-five percent of CTA transplant patients experience at least one AR phase during the first year following transplantation, and up to 60 percent undergo multiple AR episodes. The first phase of the study is to build a predictive model of graft rejection based on non-invasive imaging and immunological biomarkers in a swine CTA model. The resulting model will be validated in human patients during the second phase. The study team hypothesizes that non-invasive imaging modalities may be combined with immunological molecular markers to build a predictive Bayesian classifier model to allow for improved monitoring and diagnosis of rejection without the need for invasive tissue biopsies in advance of clinical signs



of rejection or permanent tissue damage. A predicative model will help to identify potential novel monitoring and diagnostic tools and targets to improve treatment of CTA rejection. Imaging modalities employed include Raman Spectroscopy (RS), Infrared Thermography (IR) and visible reflectance spectroscopy (VRS) to examine compositional tissue changes, whole graft perfusion, and tissue oxygenation respectively. This study is funded by USAMRMC in support of the AFIRM II Cooperative Agreement.

The study employs a heterotopic hind-limb CTA swine model with three study groups: 1) AR, 2) standard immunosuppression, and 3) cycled immunosuppression. Daily digital, IR, and VRS images are collected following transplantation and the animals are monitored for rejection. At rejection, a skin biopsy is collected for RS analysis. To date, imaging studies have been completed on 15 pigs and identified potential imaging and spectroscopic markers of rejection and are currently analyzing chemokine/cytokine biomarkers. All metrics will be combined for Bayesian modeling analysis.

Concurrently, imaging of human patients will proceed at a partnering institute and skin biopsies will be collected. Once the final protocol amendment is processed by the IRB for WRAIR, human samples and imaging data will be collected and imaging analysis will proceed.

### **Improved Biomarker to Guide Surgical Care of Combat-related TBI**

TBI has been a signature wound in recent conflicts. The use of IEDs resulting in high-energy blasts and subsequent multimodal creation of extreme injury patterns not seen in previous conflicts has created enormous challenges in the medical and surgical management of these wounded Service Members. Severe TBI is often accompanied by secondary injury due to anatomic and biochemical processes and is treated with

hemicraniectomy and CSF drainage. Key decisions regarding diagnosis of vasospasm, antibiotic therapy, removal of CSF access, and bony reconstruction are made based upon examination, monitoring, lab and imaging studies, and clinical judgment. Understanding immunologic implications with a mechanistic focus directed towards clinically translatable therapeutic manipulation, and their consequences, calls for the development of accurate clinical decision support tools (CDST). Using patient-specific clinical variables combined with local and systemic biomarkers, CDST can be developed that can guide and optimize treatment in patients with severe TBI.

Researchers at the Surgical Critical Care Initiative (SC2i) at USUHS in collaboration with Emory University and funded by the DHP are developing a predictive model capable of addressing key decision points for patients with severe TBI. These key decision points include: (1) onset of vasospasm; (2) timing of removal of ventriculostomy and decision to place permanent ventriculoperitoneal shunt; (3) onset of ventriculitis/encephalitis and antibiotic utilization; and (4) timing of craniofacial reconstruction. Major objectives are to develop a repository of CSF and serum and correlate data with clinical outcomes to develop predictive models. The key research accomplishments in FY16 include: (1) the reapproval by the IRB of the study protocol; (2) engagement with the Emory Emergency Medicine and Neuroscience Department staff to improve recruitment and sample collection; and (3) successful collection, validation, and transfer of samples collected from the first five patients added to the Bioinformatics Core Services aggregated clinical and assay data. In addition, patient enrollment in the study has increased to 1-2 patients per month resulting in a cumulative enrollment of 11 patients. Furthermore, vasospasm was detected in one of the study

patients through the research-funded transcranial Doppler imaging; as a result, the patient was treated accordingly. This initial effort will serve as a roadmap for follow-on applications for biological discovery and development of next generation patient diagnostics and personalized treatments. The subsequent focus will be on detection and even prediction of deterioration before it becomes clinically apparent in TBI combat casualty patients. Leveraging both clinical and biomarker data, and using advanced machine learning techniques, this project is prospectively analyzing patient and injury-specific characteristics associated with the aforementioned complications and outcomes of interest in order to identify both significant predictors of specific outcomes as well as to identify potential general and biochemical/cellular targets for therapeutic intervention. Next generation patient diagnostics and personalized treatments that are developed for the outcomes of this study are expected to guide and optimize treatment in patients with severe TBI.

### **BrainScope Ahead® 300 System**

TBI has received increasing attention in recent years as the public is made more

aware of the long-term consequences of mTBI resulting from injuries sustained during military combat operations. The rapid and accurate identification and triage of head injured persons who are at-risk for having sustained structural brain injury and are in need of further clinical assessment represents a significant unmet public health need. In a project funded by the CCCRP, BrainScope developed the BrainScope Ahead® System. BrainScope's Ahead® technology employs EEG, a proven electrophysiological core technology, in a portable, point-of-care, non-invasive device designed to improve early identification, staging, and optimization of treatment for patients who are suspected of a TBI. The Ahead® system incorporates sophisticated classification algorithms that enable rapid assessment of a patient's brain injury, specifically identifying those patients who are likely to have a positive finding for structural brain injury visible on a CT scan of the head. Development of the next generation platform, the Ahead® 300 (Figure 7-12), was funded under the Army Rapid Innovation Fund Research Program and CCCRP. The primary objective of this study was to conduct a multi-center, prospective clinical trial (B-AHEAD III) in order to validate the clinical utility of the



**FIGURE 7-12:** Combat Medics and Physician Assistants of the 1st Brigade Combat Team of the 82nd Airborne testing the Ahead® 300 system. Photographs courtesy of Michael Singer.



Photo credit: BrainScope Company, Inc./US Army

BrainScope Ahead® 300 device for the acute identification of structural brain injuries in the mTBI population. In addition, the study sought to extend findings of the B-AHEAD II Trial in a large population to replicate and extend the previous trial using the BrainScope Ahead® 300 device. The clinical trial included 981 participants from 11 acute care emergency departments in the US. The clinical validation studies were completed in early 2016. In September 2016, the FDA granted clearance of the BrainScope Ahead® 300, the first handheld medical device for assessment of the full spectrum of TBI. Having a rapid, reliable, and sensitive assessment device to aid in the triage of patients who are suspected of a traumatically induced brain injury will lead to appropriate and timely diagnosis and subsequent medical care for affected Service Members.

#### **Tissue Data and Acquisition Protocol Biobank/Databank**

The Tissue and Data Acquisition Protocol (TDAP) developed by SC2i at USUHS is actively enrolling critically ill patients at Emory University, Duke University, and

WRNMMC. The TDAP is a standardized method for collecting all clinical data and biological specimens from critically-ill patients and healthy volunteers in support of all research initiatives approved by the SC2i. General procedures covered under this protocol include clinical sample acquisition, processing and storage, clinical data capture and storage, and the sharing of data and samples amongst SC2i partners. Through TDAP, the SC2i leverages resources in the most efficient way to maximize productivity and inform the development of numerous CDSTs across conditions associated with a high incidence of mortality and morbidity (e.g., venous thromboembolism, bacteremia/pneumonia, acute kidney injury, sepsis). The TDAP currently enrolls six to 10 patients a week (300 to 500 annually); across all sites, close to 400 patients have been enrolled since the SC2i's inception in FY14. A central, standardized means of enrolling patients that allows for post hoc analysis and sample distribution not only allows for multiple observational trials to be served with the same patient population, but through standardized



processes, allows for insights to be leveraged across observational platforms to inform the development of CDSTs in the acute care space.

### **Open Abdomen CDST**

Up to 25 percent of all trauma laparotomies require management with open abdomens. Damage control laparotomy (DCL) followed by temporary abdominal closure, resuscitation, and planned re-laparotomy is used to manage critically injured patients who cannot be closed primarily at the initial operation. No studies to date have evaluated objective criteria for predicting successful closure of the open abdomen after DCL; the appropriate timing of abdominal closure or coverage has yet to be determined. Leveraging its growing biobank/databank of trauma patients under the TDAP, researchers at SC2i at USUHS are developing a CDST to inform the timing of delayed fascial closure after DCL. Identifying risk factors for delayed fascial closure may help to avoid the complications of multiple attempts to close and optimize the chance of a successful planned staged ventral hernia; this could shorten time to recovery and potentially prevent some of the complications seen after DCL in this population. Preliminary findings indicate elevated peak serum and wound procalcitonin levels may be associated with delayed fascial closure after DCL. This challenge is particularly relevant to combat casualty care; the deployment of the aforementioned CDST, once validated through a clinical trial, has the potential to dramatically improve outcomes and lower resources utilization for the MHS.

### **Evidence-based Multimodal Neurodiagnostic Imaging of TBI and PTSD**

Funding from the PH/TBIRP managed by CDMRP was awarded to researchers at Saint Louis University to conduct this study in collaboration with colleagues at the University of Missouri-Saint Louis. The

primary objective of this study is to compare three cohorts: (1) healthy brains; (2) brains of civilians with TBI; and (3) brains of Service Members with combat-related TBI; to identify correlations between abnormal imaging parameters with neurorehabilitation potential using advanced neurological imaging. The secondary objectives include comparing combat TBI (blast-induced) to civilian TBI (primarily acceleration/deceleration injuries) to normal brains to precisely estimate the incidence and prevalence of structural and functional abnormalities occurring during deployment in a combat area and elucidating the group differences in combat versus non-combat TBI using multimodal neuroimaging diagnostic tools. In 2015 the research team published results from evaluation of the MRIs that demonstrated cortical thinning in the context of chronic blast-related TBI in Military Veterans with comorbid psychiatric conditions.<sup>58</sup> The research team was invited to submit a manuscript for a special issue of the journal *Behavioral Sciences and the Law* focused on TBI. Both Veteran and civilian TBI groups exhibited limited neuropsychological impairment, relative to the healthy controls.<sup>59</sup> The Veteran TBI group exhibited pronounced neuropsychiatric symptomology compared with the other groups. The implications of these findings were discussed for neuropsychological evaluation in the context of disability and litigation. The results may have implications for future clinical evaluation and treatment of Service Members.

### **Chemokine Ligand 2 Levels in CSF as an Early-response Biomarker for Blast-Induced Neurotrauma**

The neuroinflammatory response is an early pivotal immune process following brain injury. The inflammatory mediator chemokine ligand 2 (CCL2), also known as monocyte chemoattractant protein-1 (MCP-1),

has been implicated in the pathogenesis of brain ischemia, Alzheimer's disease, and other neurodegenerative diseases.<sup>60</sup> Using a rat model of single and repeated blast exposures in a shock tube, researchers at the WRAIR investigated the time-course of changes in MCP-1/CCL2 level in the CSF and blood. Significantly increased concentrations of CCL2 in CSF were evident by one hour after blast exposure and persisted over 24 hours with peak levels measured at six hours post-injury. The increased levels of CCL2 in CSF corresponded with both the number and the intensities of BOP and were also commensurate with the extent of neuro-motor impairment and neuropathological abnormalities resulting from these exposures. CCL2 levels in CSF and in plasma were tightly correlated with the levels of CCL2 mRNA in the cerebellum, the brain region most consistently neuropathologically disrupted by blast. In view of the roles of CCL2 that have been implicated in multiple neurodegenerative disorders, it is likely that the sustained high levels of CCL2 and the increased expression of its main receptor CCR2 in the brain after blast may similarly contribute to neurodegenerative processes after blast exposure. In addition, the markedly elevated concentration of CCL2 in CSF might be a candidate early-response biomarker for diagnosis and prognosis of blast-induced TBI. Since cytokines such as CCL2 are known to have both beneficial and detrimental effects in the milieu of the injured brain, and contribute to degenerative and regenerative processes, the timing of these responses is critical to their neurobiological importance. By revealing important neurobiological mechanisms that underlie BOP-induced brain injury, these experiments will provide valuable insights into detection and therapeutic countermeasures for affected Service Members.

### **Novel Smart Catheter for Multimodal Monitoring of the Head-Injured Warrior**

TBI is a major focus of combat casualty care, as it remains a principal cause of mortality and morbidity in the military setting. This is especially because of the enemy's use of low cost, yet powerful, IEDs. The critical period during which the injured brain is very vulnerable to secondary injury is approximately one week after severe head trauma; for severe blast-related TBI, ischemic insults may even persist for several weeks. Current standard-of-care for severely brain injured patients calls for monitoring intracranial pressure (ICP) and possibly brain oxygenation, using multiple devices. Unfortunately, the use of this technology has not kept pace and has remained essentially unchanged for two decades. One cannot overstate the need for a compact but sophisticated neuromonitoring device which can be used in hospitals or during transport and is capable of allowing for targeted interventions before irreversible brain damage occurs. Collaborators at the Feinstein Institute for Medical Research and the University of Cincinnati received funding from the PH/TBIRP managed by CDMRP to develop a single, novel, multimodality neuromonitoring device, or 'smart catheter'. The researchers developed and took this catheter through initial design, small scale production, laboratory refinement, and early animal testing. Recent studies have shown that a phenomenon known as spreading depolarization may be the pathophysiological basis of neurological deterioration in severe TBI patients.<sup>61-63</sup> However, the technology to study this phenomenon and to understand what causes it in humans has been limited until this catheter was developed. This one-of-a-kind catheter was successfully designed and microfabricated with seven microsensors (ICP, temperature, cerebral blood flow (CBF), oxygen tension, glucose,

lactate, and electrocorticograph) using a flexible polyimide substrate that was spirally rolled to form a catheter for multimodal sensing of critical intracerebral variables. The function and performance of the complete system was tested and validated in both rat and pig animal models.<sup>64-66</sup> Both the individual sensing technologies as well as the capabilities to monitor multiple variables represent tremendous advances in brain monitoring and neuroscience. The sensors developed individually or in various combinations, hold great commercialization potential for biomedical research applications since, presently, combined probes are not commercially available. Furthermore, the individual sensing technologies, such as the quantitative CBF monitor, represent significant advances compared to the best monitoring techniques available to biomedical researchers today, and also have application for other tissues besides the nervous system. The collaborating institutions have filed several patent applications covering the technology developed by the researchers and a patent has been issued for the ‘smart catheter’ (patent number 8,628,493). Members of the research team received two awards at the 2016 Annual Meeting of the American Academy of Neurological Surgeons: the Synthes Cerebrovascular Section Resident/Fellow Award and the ThinkFirst Head Injury Prevention Presentation Award.<sup>67,68</sup>

The ability to understand the dynamic and unique pathophysiology of severe neurotrauma from explosive blasts using an advanced ‘smart catheter’ advances the field of neurocritical care which is important to the care of critically injured Service Members who are being transported across long distances during periods of maximum vulnerability to secondary injury.

### **A Pilot Study of Molecular Neuroimaging of CBF Abnormalities due to TBI in a Swine Model**

The goal of this research is to discover a molecular neuroimaging biomarker that can be used to detect secondary TBI during the acute phase of injury. Secondary TBI is more prevalent than primary TBI, is not detected with CT and MRI, and accounts for the majority of the morbidity and medical costs associated with TBI. The presentation of secondary TBI is subtle and often presents with nonspecific symptoms such as headache, confusion, cognitive deficits, and PTSD. Without an accurate diagnostic test, physicians cannot appropriately treat secondary TBI, the potential for a recovery is reduced, and Service Members effectiveness is reduced. Researchers at the David Grant US Air Force Medical Center propose to test a radioactive tracer that can capture an image of the brain shortly after the injury and can identify Service Members who need immediate medical attention for secondary TBI. Following brain injury in a porcine model (*Sus scrofa*), 25 millicurie of Technetium-99m (<sup>99m</sup>Tc) hexamethylpropyleneamine oxime was injected intravenously within one minute, at one hour, and four hours after impact. A Single Photon Emission Computed Tomography/CT scanner can then take delayed pictures of the radiotracer distribution in the brain. Abnormalities in the radiotracer distribution represent areas of injured brain tissues and can be used to detect acute TBI. Initial study results are promising and an invention disclosure has been submitted.

### **Incapacitation Prediction for Readiness in Expeditionary Domains - an Integrated Computational Tool (I-PREDICT)**

Current challenges exist in anticipating the human injury response to physical stressors associated with blast exposure, such as



blast and acceleration forces, vibration, and blunt traumas. To address these challenges, researchers at the ONR have developed an integrated physiologically-relevant human body model and associated software tool titled “Incapacitation Prediction for Readiness in Expeditionary Domains - an Integrated Computational Tool (I-PREDICT)”. I-PREDICT uses a model based on material properties of human tissues and experimentally derived strain rates to predict injury outcomes in response to specific blast related stressors. The purpose of this predictive modeling tool is to predict the probability of immediate incapacitation and short-term disability in response to multiple physical stressors contributing to medical response planning, injury prevention, and treatment planning. In addition, I-PREDICT can be utilized to perform preliminary design, testing, and validation of PPE contributing to injury mitigation planning capabilities. Predictive modeling tools such as I-PREDICT will contribute to reduced injuries, substantial cost and time savings, and the development of more effective PPE.

#### **Rapid Field Assessment of Visual Acuity**

Current techniques to assess vision impairments on the battlefield consist of simply asking the Service Member questions regarding any changes to vision or to count how many fingers the medic is holding up. This gross assessment of potential vision impairments often leads to inaccurate estimations of visual damage. VCE researchers in conjunction with Madigan Army Medical Center and WRNMMC Departments of Ophthalmology researchers have developed a rapid vision assessment tool for use by combat medics and first responders. The purpose of this work was to devise a simple method to rapidly assess the visual acuity of a casualty on the battlefield by utilizing an approach that will yield more accurate and reliable visual measurements

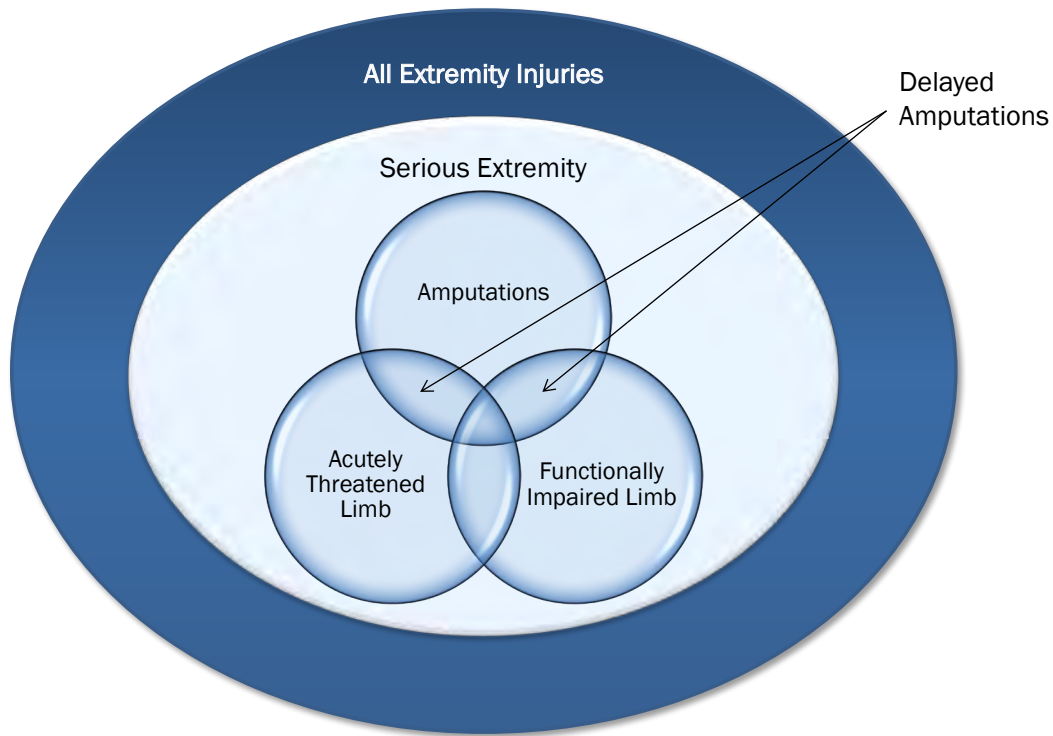
than the current techniques. As a result of the development of this tool, visual acuity screening at the point of injury need not be delayed for lack of formal vision screening cards. Further work is planned to assess the adaptability and validity of this effort. The rapid vision assessment tool was presented at MHSRS in August 2016.<sup>69</sup>

### **Extremity Injury**

#### **The Association of Specific Serious Lower Extremity Injuries with Delayed Amputation**

Numerous studies have reported high proportions of extremity injuries in OIF and OEF, with estimates between 41 percent and 54 percent of injuries. Despite medical interventions to preserve the viability and functionality of the injured limb(s), delayed amputations and long-term impairments may occur as a result of these injuries. The goal of this analysis, requested and funded by EACE, was to determine whether specific acute lower extremity injuries are associated with delayed lower extremity amputations. The NHRC’s EMED was queried for battle-related lower extremity injuries between 2003 and 2014, which resulted in 9,592 injury episodes. The AIS was used to categorize the lower extremity injuries by severity and the maximum lower extremity AIS level for each injury episode was determined. All episodes with a maximum lower extremity AIS of 1, as well as individuals with amputations occurring on the day of injury were excluded. The final sample was 3,509 Service Members, with at least one lower extremity injury having an AIS of 2 or greater. The frequency of specific lower extremity fractures (femur, tibia, fibula, calcaneus, talus, or navicular) as well as lower extremity nerve and vessel injury was determined. The association of each injury and specific injury combinations with a delayed amputation (amputation occurring after date of injury) was calculated (Figure 7-13). A delayed amputation was

**FIGURE 7-13:** Extremity Injury spectrum (not to scale) provided by Susan L. Eskridge, PT Ph.D.



identified in 308 (8.8 percent) injured Service Members in the sample. The delayed amputation and no amputation groups did not differ in average age at the time of injury (25.7 years versus 26.0 years) or branch of Service (Army, 67.2 percent versus 63.6 percent), and the majority of the injury episodes were blast related (84.1 percent versus 72.3 percent). There was no difference between the groups in mean or categorized Injury Severity Score (ISS; 14.9 versus 11.7) with the majority of both groups having an ISS greater than 9. The most frequent fractures were of the tibia (29.5 percent) and fibula (25.2 percent), yet the highest rates of delayed amputation were in Service Members with navicular (35.9 percent), talus (29.7 percent), or calcaneus (27.9 percent) fractures. Logistic regression with paired independent variables was carried out to examine the impact of multiple injuries on the odds of delayed amputation. The odds of amputation were greatest in the combination injuries of calcaneus fracture and lower extremity nerve injury, calcaneal fracture and lower extremity vessel injury, and calcaneus and tibia fractures. Although

the most common fracture locations in this group of combat injuries were in the tibia and fibula; fractures of the navicular, talus, and calcaneus were more likely to result in a delayed amputation. The odds of delayed amputation increased substantially with specific injury combinations. Understanding the odds of amputation with specific acute injuries may guide clinical decision making in the acute care period.<sup>70</sup> Further analyses should investigate the role that other injuries and acute complications play into the risk of amputation.

#### **Venous Thromboembolism CDST**

Combat casualties have a relatively high incidence of venous thromboembolism (VTE); rates of VTE in the combat wounded can reach up to 28 percent and complications are severe, including death. Building on a retrospective review of 560 consecutive combat casualties from October 2010 to November 2012 admitted to a MTF in the US, the SC2i at USUHS is developing a CDST that can predict those at the highest risk for developing VTE. The work of the SC2i in this space suggests

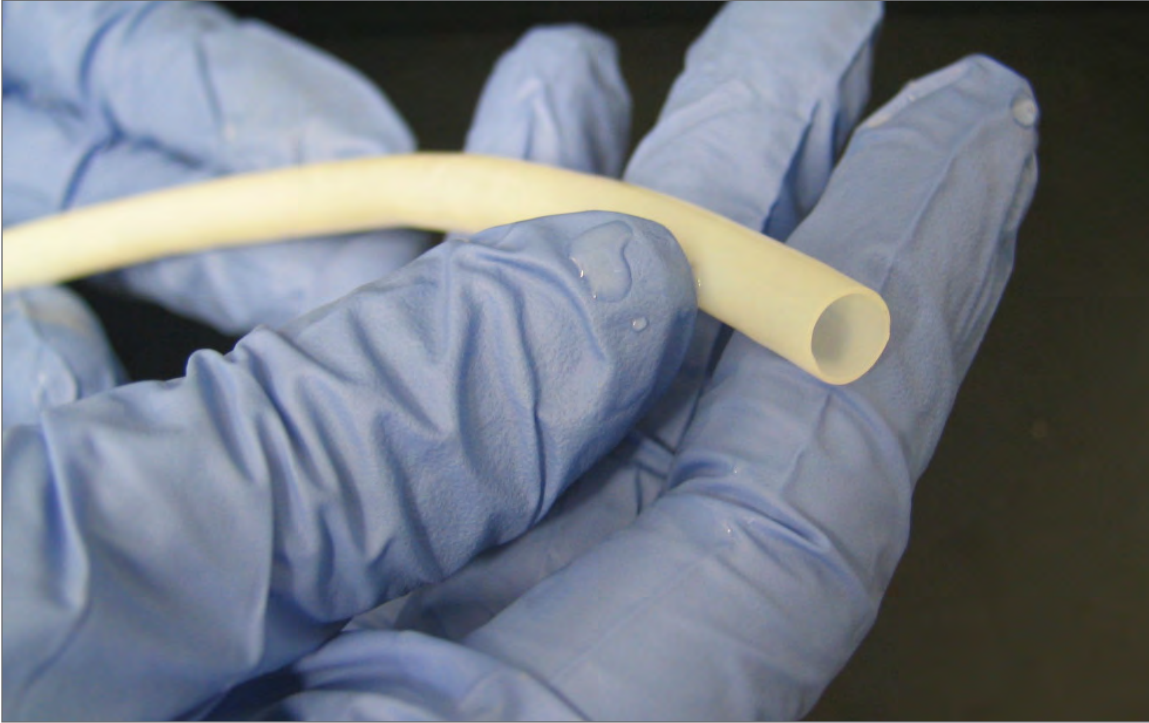
that a more refined predictive model is needed to accurately apply resources with regards to VTE screening and prophylaxis. The development of this tool is currently under way, using both clinical and biomarker variables to predict incidences of VTE, and initial models show encouraging findings with promising area under the curve (AUC) and high net benefit decision curve analysis. SC2i will continue to develop this tool by incorporating machine learning algorithms and heterogeneous data such as systemic immune protein biomarkers that will help to establish a better approach in predicting VTE events in combat trauma patients. The development of a predictive algorithm is expected to have a substantial and measurable impact on both clinical outcomes and resource utilization for the MHS by assisting in guiding surveillance and prophylaxis of VTE. Furthermore, development of a model to predict VTE will have direct translatability in both military and civilian healthcare settings.

### **Tissue-engineered Vascular Grafts**

It is estimated that 2,500 of the nearly 60,000 injured Service Members (roughly four percent) suffered a vascular injury amenable to repair during the period of the recent wars. The rate of traumatic vascular injury requiring surgical intervention has been higher in recent years due to the use of tourniquets and hemostatic agents compared to historical data (2005 versus 1965). Vascular injury as a proportion of overall trauma has increased from one to two percent in the American Civil War to about 12 percent during recent conflicts in Iraq and Afghanistan. In 2013, the DoD highlighted a critical need for “... managing disruption and hemorrhage from the junctional regions between the torso and the extremities” in injuries that impact the vasculature (USAMRMC Program Announcement for Forward Surgical and En Route Care, Funding Opportunity

Number W81XWH-13-CCCJPC6-FSERC). Autologous vein grafts currently remain the standard of care, with the saphenous vein being the primary donor site, despite the difficulty, or impossibility in many instances. The saphenous vein is often too small for an adequate repair, or difficult for a less experienced surgeon to locate. Synthetic vascular reconstruction using synthetic vascular grafts made from Teflon polytetrafluoroethylene (PTFE)/Dacron is relatively contraindicated, since IED wounds are always “dirty”, and bacteria in the wound can colonize the synthetic graft, causing abscesses and sepsis, therefore there is a need for alternative conduit to PTFE. The effort to salvage limb tissue may be hampered by damage to the vasculature that prevents re-establishment of blood flow to preserve the limb, necessitating amputation. The Human Acellular Vessel (HAV; see Figure 7-14) from Humacyte<sup>®</sup>, Inc. is a decellularized, off-the-shelf vascular conduit capable of tolerating high pressure perfusion, and which is rapidly infiltrated by recipient cells.<sup>71</sup> Humacyte<sup>®</sup> has developed this important new technology by culturing banked human cells in bioreactors in the laboratory followed by decellularizing the construct to produce a mechanically strong, tissue-based graft that is non-immunogenic and can be implanted into any recipient. Humacyte<sup>®</sup> is attempting to obtain a primary indication in a relatively low risk application as a hemodialysis (HD) shunt.<sup>72,73</sup> This effort will be followed by an indication for arterial reconstruction bypass. These HAVs can be shipped to hospitals and field locations, and can be stored until needed. Humacyte<sup>®</sup> began FDA-regulated clinical trials for the HD indication in December 2012, and the shunt has been implanted in more than 100 patients with no immune reactions reported. The product is currently in a Phase 3 clinical trial for this indication with Biologic License Application filing with FDA projected for FY18. Further,





**FIGURE 7-14:** Humacyte's HAV

there has been no structural degradation, and only one graft infection reported to date from the clinical development program. A reduction in infection rates has also been demonstrated in a murine model of bacterial graft contamination with lower infection rates observed compared to synthetic graft material. The grafts are also self-healing making them amenable to the frequent re-cannulation required for HD. The product is a first-in-man regenerative medicine product, and the HD indication was attempted first in a lower risk patient population with less urgent need for intervention. However, the supporting systems and processes developed (quality, manufacturing, shipping) will support all indications. The effort to extend application to arterial reconstruction was initiated in October 2013 with a study of above-knee femoral-popliteal bypass grafts in Poland. A 20-subject study has been successfully completed. Army funded efforts to gain FDA approval for the arterial graft in the US have been ongoing through the AFIRM II consortium, and an Investigational New Drug

(IND) “safe to proceed” letter was received from the FDA in July 2016.

#### **Woundx CDST**

Complex war wounds require aggressive surgical care. Serial debridement procedures are performed to remove devitalized tissue and decrease bacterial load. While high-pressure irrigation and negative pressure therapy with vacuum-assisted closure application have improved wound management, the basic surgical decision regarding appropriate timing of war wound closure or coverage remains subjective. In the context of high rates (15-20 percent) of wound dehiscence in the combat wounded, researchers at SC2i at USUHS have developed a biomarker based CDST to assist in the decisions on timing of wound closure.<sup>74</sup> Wound dehiscence is defined as loss of greater than 10 percent of a skin graft, dehiscence of a primary wound closure requiring debridement, failure of a tissue flap requiring repeat operative intervention, or need for subsequent amputation. The consequences of these complications are many: lengthy delays

to definitive wound closure, increased pain, nutritional setbacks, higher costs, and further loss of function if an amputation level should be raised to save a Service Member's life. This CDST was developed to assist surgeons in determining the optimal timing of traumatic wound closure. The model has been tested/validated internally and performs well (AUC of 0.84 and 0.87 for dehisced/heal). Grounded in research on datasets from civilian as well as military patients using clinical and biomarker data, this CDST model is expected to reduce wound dehiscence rates from the current rate of 15 percent to only 5 percent. Achieving this goal will produce multiple benefits, including decreased pain, fewer complications, better outcomes, and lower net costs (e.g., reducing the need for repeated operations, hospital-acquired infections, and length-of-stay in the intensive care unit or on the General Ward). It should also increase the likelihood that a severely injured Service Member can eventually RTD. Termed 'WoundX', this CDST has direct applicability in both military and civilian healthcare systems as similar wound failure rates occur in both settings. In short, the WoundX CDST will decrease the time from injury to successful wound closure, thereby improving clinical outcomes and lowering costs for the MHS (estimated savings of \$60,000 per patient). An Investigational Device Exemption (IDE) package is being finalized for submission to the FDA, ahead of launching a clinical trial to validate the clinical utility of this CDST.

### **Incidence and Clinical Correlates of VTE after Combat-related Amputation**

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are potentially life-threatening complications that have not been well studied after traumatic limb amputations caused by combat injury. This is particularly true for US Service Members who sustained severe blast injuries causing high-level and often

multiple limb amputations during the recent conflicts, 2009–2011. Researchers at the NHRC and NMCSO—with funding from EACE and the Navy Bureau of Medicine and Surgery (BUMED) Wounded, Ill, and Injured (WII) Program—reviewed casualty records in NHRC's EMED. The objective was to determine the incidence, post-injury timing, and risk factors for DVT and PE following combat-related limb amputations. Injuries and treatments documented by providers at Role 2 or 3 facilities in Iraq or Afghanistan were reviewed for 366 patients who sustained traumatic amputations proximal to the wrist or ankle. The research team recorded the ISS, number of blood transfusions during initial 24 hours, duration of mechanical ventilation, intensive care unit length of stay, primary outcome, and diagnoses of DVT or PE through 12 months post-injury. Findings included that 28 percent of patients had DVT and/or PE diagnoses, including 16 percent who had a PE.<sup>75</sup> Approximately two thirds of DVT/PE cases occurred within 10 days of injury and nearly 90 percent occurred during the first 60 days post-injury. Increased number of ventilator days and units of blood transfused were significantly associated with increased likelihood of DVT. Increasing units of fresh frozen plasma (FFP) transfused was significantly associated with increased likelihood of PE. Prophylactic medication significantly decreased the likelihood of DVT and PE. The present study helps providers identify early treatment factors that increase patient risk for the life-threatening complications of DVT and PE. The prevalence of PE and DVT was relatively high after traumatic amputation. Therefore, post-injury surveillance and use of prophylactic medication is indicated for this population. Identification of risk factors for DVT and PE helps focus acute care resources more efficiently on patients who are most likely to develop these complications.

### **Characterization and Optimization of Auto-transplantation and Allo-transplantation of Free Composite Tissues for Reconstruction of Battlefield Injuries**

Modern battlefield injuries often produce devastating extremity and craniofacial injuries, for example extremity and craniofacial injuries account for greater than 85 percent of all injuries in OIF/OEF. Current methods of reconstruction often fall short of restoring form and function. Surgical reconstruction of these injuries using free composite tissue auto-/allo-transplantation can be used to ameliorate ischemia/reperfusion injury and maximize reconstructive reliability; however, clinical adoption of vascularized composite allotransplantation (VCA) is limited by the need for systemic immunosuppression, with associated morbidity and mortality. Small-animal models lack the biological fidelity and preclinical relevance to enable translation of immunologic insights to humans. Large-animal models have been described; however, limitations persist, including the inability of heterotopic models to evaluate functional nerve regeneration, and the sensitivity of primates to toxicity of immunosuppressive drugs. Researchers from the US Army Institute of Surgical Research (USAISR) and 59th Medical Wing in collaboration with researchers from the Royal Centre for Defence Medicine, Birmingham, England the Department of Surgery at the University of Texas Health Science Center at San Antonio, and the University of Pittsburgh Medical Center developed a novel orthotopic porcine limb transplant model that has broad applicability and translational relevance to both immunologic and functional outcomes after VCA. In this model, pigs underwent amputation at a level corresponding to the mid forearm. Replantation or transplantation of grafts was performed by plate fixation of the radio-ulna, microsurgical repair of brachial artery and median nerve, and

extensor and flexor tendon repairs. Viability of replants was monitored clinically and radiologically. Transplants were monitored for clinicopathologic signs of rejection. Animals mobilized freely postoperatively. The researchers found that replantations remained viable until the endpoint of 14 days. Transplants developed Banff Grade 4 AR by postoperative day seven. Doppler sonography and angiography confirmed vascular patency. Serial biopsy specimens of skin and histopathology of replants at endpoint confirmed tissue viability and bone healing. In conclusion, an orthotopic load-bearing porcine forelimb VCA model was successfully established. Technical, procedural, and logistic considerations were optimized to allow model use for immunologic, bone healing, functional nerve regeneration, and other translational studies. This research was published in *Plastic and Reconstructive Surgery* in 2016<sup>76</sup> and is expected to improve reliability of CTA, providing translatable principles for immediate application to battlefield injuries in the expeditionary setting and for restoration of long-term near-normal form and function.

### **Hemorrhage Control and Resuscitation**

#### **Cryopreserved Platelets (CPP) Phase 1 Safety Trial Successfully Completed**

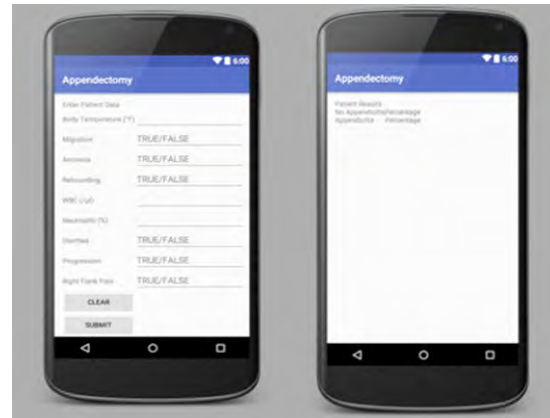
Platelets are a vital component for treatment of severe bleeding but cannot be reliably supplied in liquid form to the battlefield, nor can they be fully pathogen tested prior to transfusion. From 2001-2011 up to 26 percent (~1,075 deaths) of total pre-MTF combat deaths may have been potentially survivable and 91 percent of these were due to hemorrhage. CPP will be fully pathogen tested and will potentially allow treatment closer to the point of injury (further forward on the battlefield). The US Army Medical Materiel Development Activity (USAMMDA) completed enrollment of the CPP multi-site dose escalation Phase 1 safety trial on 12



July 2016. The successful Phase 1 safety trial compared CPP to the current standard of care, room temperature liquid stored platelets, in thrombocytopenic cancer patients. A Phase 2 efficacy study is expected to start enrollment in FY17. The USAISR is conducting studies of treatment of combined blast/hemorrhage with complement inhibitors in animal models under DHP funding.

### **Massive Transfusion Protocol (MTP) Smartphone Application: A Clinical Trial**

Because massive transfusions are resource-intensive and expensive, they require quick and accurate decision-making. In FY14, researchers at SC2i at USUHS began work on a MTP Smartphone application (Figure 7-15) to prospectively evaluate accuracy in predicting the need for massive transfusion in critically injured patients. As such, this clinical scenario is uniquely suited for a CDST, since accuracy and efficiency can result in improved patient outcomes and cost/logistical savings to the institution. The MTP Smartphone application allows for the accurate prediction of who may require a massive transfusion based on a sophisticated statistical model created using admission variables readily available to the clinician at the bedside. The coordination of a MTP is a complex and multi-disciplinary effort that requires both significant oversight as well as the use of a large amount of human and blood bank resources. The MTP Smartphone application has the potential to make this process less complex and more accurate, thereby improving outcomes for Service Members and reducing logistical burdens by eliminating the need for massive transfusion by approximately 15 percent.<sup>77</sup> MTPs, as part of a damage control resuscitation paradigm, have been shown in multiple military and civilian series to improve patient outcomes. This protocol could prospectively evaluate accuracy in predicting the need for a massive transfusion in critically injured patients,



**FIGURE 7-15:** Mobile application predicting the need for a massive transfusion

thereby reducing both the risk of over-transfusions and the need for blood products (e.g., logistical savings). In FY14, the SC2i supported the development and deployment of a Smartphone application to prospectively evaluate accuracy in predicting the need for massive transfusion in critically injured patients. With funding from SC2i, Emory University's Department of Surgery has deployed SC2i's MTP Smartphone application at Grady Memorial Hospital, a Level I trauma center certified by the Georgia Department of Public Health, to treat patients from the Atlanta metropolitan region and to date has enrolled over 350 patients in the MTP clinical trial. Future work includes additional analysis of the initial findings, incorporation of blood bank data, and calibration of the model for clinical use.

### **Freeze Dried Plasma IND Application Submitted to FDA**

FFP is a vital component for successful management of severe bleeding. Up to 30 percent of FFP supplied to the battlefield is unusable because of bag breakage during shipping and because of outdating after thawing (product expiration). Current doctrine does not position FFP forward of role of care -3 because of freezer requirements. Freeze Dried Plasma (FDP) will reduce waste of plasma by eliminating

breakage and outdating after thawing and will reduce power, weight, and cube required for battlefield positioning of plasma by reducing or eliminating associated freezer requirements for FFP. FDP can be reconstituted (to return to liquid) in less than five minutes with sterile water for injection (FFP takes 25-35 minutes to thaw), thereby making the plasma available for transfusion virtually on demand. Most importantly FDP will permit positioning of plasma at more forward battlefield locations closer to the point of injury, potentially improving the clinical outcomes associated with severe bleeding. USAMMDA plans to submit the FDP IND application to the FDA in early FY17. USAMMDA has an ongoing Cooperative Research and Development Agreement (CRADA) with Vascular Solutions Inc. for the development of FDP. Under the terms of the CRADA, Vascular Solutions is responsible for conducting all of the manufacturing aspects of the FDP product development effort while USAMMDA conducts all of the required clinical testing under a US Army Office of the Surgeon General (OTSG)-sponsored IND. The Phase 1 clinical trial is expected to begin in December 2016.

### **STOP THE BLEED Campaign**

A person who is bleeding can die from blood loss within five minutes; therefore, it is important to act quickly to stop the blood loss. The STOP THE BLEED Campaign is sponsored by a partnership between the CCCRP and the National Security Council. Based upon a decade of research by the US Military to identify and mitigate combat-related morbidity and mortality, this initiative represents a visible example of the ways that military lessons from war are being actively translated to the civilian community to improve public safety and save lives. The nationwide campaign seeks to increase the public's understanding of its own capacity to respond to matters of trauma and render life-saving aid, ultimately resulting in a more confident, empowered, and resilient nation.<sup>78</sup> This effort has culminated in a logo licensing effort led by the CCCRP that

created a logo (Figure 7-16), as well as a style guide and series of web-related presentations. The purpose of the licensing effort is to allow organizations and institutions to license the STOP THE BLEED graphics package from the DoD at no cost, and then apply the graphics to their educational outreach in any manner they see fit. So far, more than 65 organizations are currently participating in the campaign having incorporated the graphics package into their educational outreach programs. Specifically, this campaign stresses that almost anything can help stem the tide of hemorrhagic bleeding; a tourniquet, a belt, or even your hand. Therefore, the STOP THE BLEED logo serves as both *a reminder and a symbol that everybody has the capacity to help somebody*. For additional information on the campaign, please see the CCCRP official website ([https://ccc.amedd.army.mil/Pages/Stop\\_the\\_Bleed.aspx](https://ccc.amedd.army.mil/Pages/Stop_the_Bleed.aspx)).



**FIGURE 7-16:** The Stop the Bleed Logo

### **Injury to Sensory Systems**

#### **Olfactory Deficiency: A Marker of TBI in US Service Members**

This study is funded by the DMRDP managed by CDMRP and conducted by investigators at WRNMMC. The objective of this study is to determine whether a structured and quantitative assessment of differential olfactory performance—recognized between a blast-injured TBI group and a demographically comparable blast-injured control group—can serve as a reliable antecedent marker for preclinical detection of intracranial neurotrauma. We prospectively and consecutively enrolled 231 polytrauma inpatients, acutely injured from explosions during combat operations in either Afghanistan or Iraq and requiring immediate stateside evacuation and sequential admission to WRNMMC, a tertiary care medical center over

a two and a half year period (Figure 7-17). This study correlates olfactometric scores with both contemporaneous neuroimaging findings as well as the clinical diagnosis of TBI, tabulates population-specific incidence data, and investigates return of olfactory function.<sup>79</sup> The study team found that the olfactometric score predicted abnormal neuroimaging significantly better than chance alone. Normosmia was present in all Service Members with mTBI (e.g., concussion) and all control subjects (Figure 7-18). Service Members with radiographic evidence of frontal lobe injuries were three times more likely to have olfactory impairment than Service Members with injuries to other brain regions (relative risk 3.0, 95 percent Confidence Interval (CI) 0.98–9.14). Normalization of scores occurred in all anosmic Service Members available for follow-up testing. The conclusion is that quantitative identification olfactometry has limited sensitivity but high specificity as a marker for detecting acute structural neuropathology from trauma. When considering whether to order advanced neuroimaging, a functional disturbance with central olfactory impairment should be regarded as an important tool to inform the decision process. The clinical trial within the military cohort has produced important clinical and scientific information, which is being used to support a Phase 2 trial in an analogous civilian cohort. The research team is developing a Class II medical device with FDA oversight that will be tested in a civilian trauma cohort through a clinical trial in partnership with the University of California, San Francisco. This test could serve as a field/prehospital screening for TBI in US Troops.

### **Comparison of Ocular Injury Surgical Simulator Systems to Live Tissue Training When Training Military Ophthalmologists**

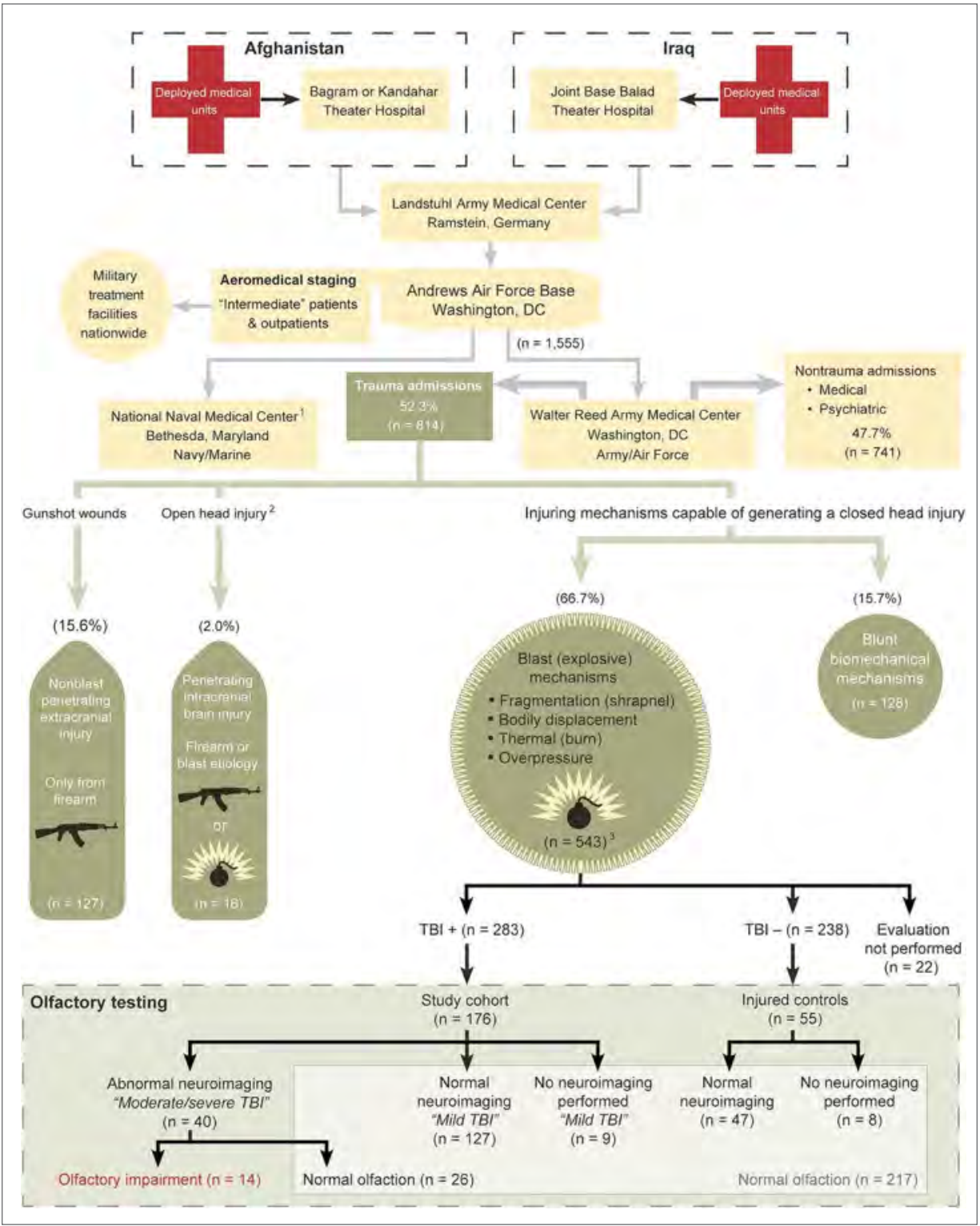
The Tri-service Ocular Trauma Skills Laboratory (TOTSL) at USUHS is an annual training environment for all military ophthalmology residents which is

geared to close the CRM RP training gap of “inadequate vision care education, training, and simulation.” Over a four year period, up to 125 Ophthalmology residents (second and third year residents) and 48 Ophthalmology faculty members participating in the Tri-service Ocular Trauma Course at USUHS will participate in this research study at the TOTSL. This study is funded by the CRM RP and managed by the CDMRP. Since initiation of the TOTSL, researchers have enrolled 91 residents and 28 faculty members. In FY16, 50 subjects were enrolled to compare the efficacy of time-limited training on surgical performance of novice (n=34) and expert (n=16) military ophthalmologists, with an emphasis on objectively assessing the role of live tissue versus simulation in the curriculum. To date, corneal laceration repairs improve following structured training, but there is some variability in surgical improvement in eyelid laceration repairs. Corneal laceration research data was presented at the 2016 MHSRS.<sup>80</sup> Simulation-based training facilitates initial surgical skill acquisition in ophthalmology. The integration of surgical simulation systems in military ocular trauma training programs benefits participants as evidenced by improved performance and positive feedback from trainees post training. Also, as a component of the TOTSL, in FY16, instructors included new topics on TBI, visual dysfunction, psychological impacts of vision loss, and blast biomechanics as core components of the curriculum. Given that the Ocular Trauma Course is the only controlled environment for ocular trauma training, an emphasis must be placed on expanding readiness training, both in number of training cycles and locations. Improved training will result in highly skilled surgeons performing complex ocular surgeries in a deployed setting improving outcomes for Service Members.

### **Assessment and Treatment of Blast-induced Auditory and Vestibular Injuries**

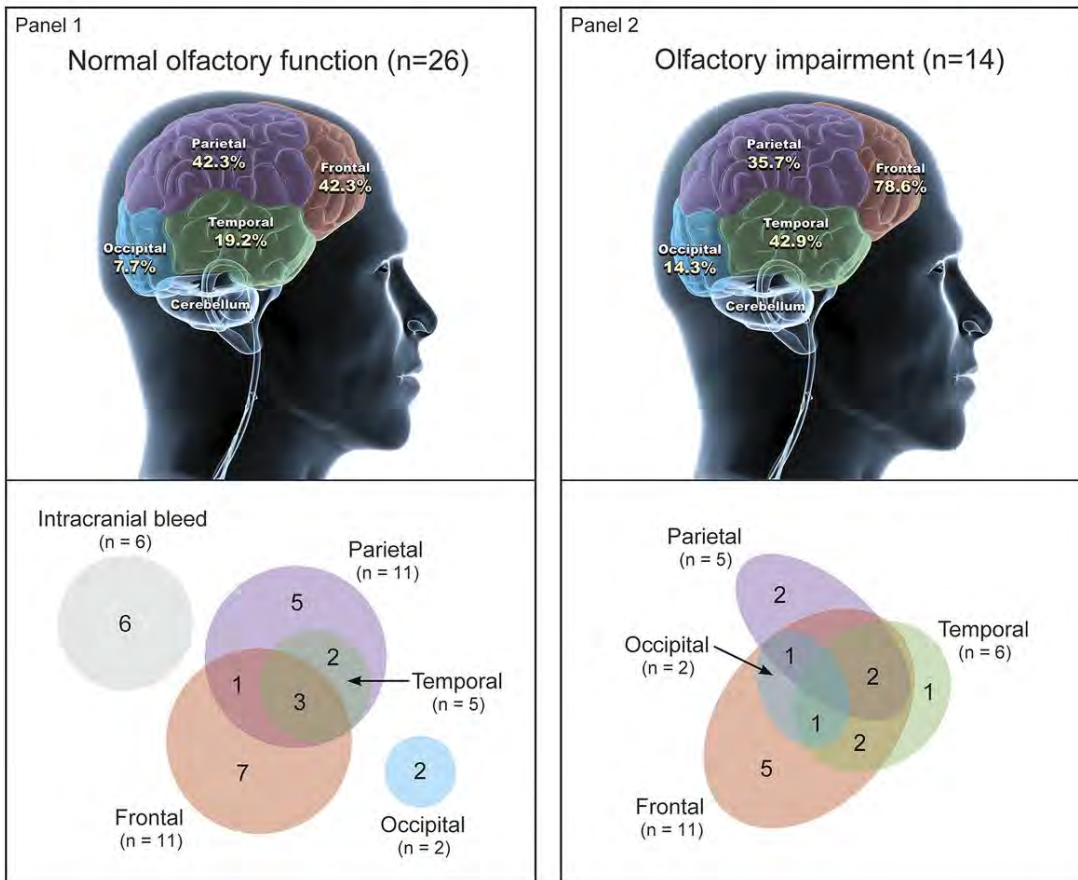
The most common symptoms after blast





**FIGURE 7-17:** Combat Casualty Care Pathway: Interhospital transfer of inpatients from Afghanistan and Iraq to Walter Reed Army Medical Center US Air Force Transportation Regulating Command and Control Evacuation System aircrew mission manifests provided longitudinal tracking of all patient movements from the combat zones to our hospital.

Location of brain injury	Normal olfactory function (n = 26)	Olfactory impairment (n = 14)	p value
Frontal	11 (42.3%)	11 (78.6%)	0.046
Parietal	11 (42.3%)	5 (35.7%)	0.746
Temporal	5 (19.2%)	6 (42.9%)	0.147
Occipital	2 (7.7%)	2 (14.3%)	0.602
Multifocal	6 (23.1%)	6 (42.9%)	0.281
Frontal OR temporal	13 (50.0%)	12 (85.7%)	0.040
Frontal AND temporal	3 (11.5%)	5 (35.7%)	0.102



**FIGURE 7-18:** Troops with abnormal neuroimaging: Location of injury and its association with olfactory performance and multifocality (n = 40) For specific brain regions, data do not sum to 100% because more than one region could be affected.

exposure are headaches, hearing loss, balance problems, and dizziness which strongly suggest blast waves caused injury/impairment to the structure of the inner ear and neuronal encoding of sound. Researchers at the WRAIR have developed complementary rodent models to characterize the effects of blast exposure on both the auditory and vestibular organs of the inner ear in conjunction with assessments of

the disruptions in connections among the brain structures involved in auditory and vestibular signal processing. In collaboration with the National Institute for Deafness and Other Communication Disorders and the Lieber Institute for Brain Development at the Johns Hopkins School of Medicine, researchers at WRAIR are developing strategies for mitigating or reversing auditory/vestibular injury that originates

from damage to mechanosensory hair cells and brain structures. Using an ABS, which produces a high fidelity recreation of BOP in the laboratory; rodents are exposed to shock waves to characterize the etiology of blast-induced hearing loss and balance disorders. Along with histopathological and neurochemical assessments and the quantification and characterization of the auditory and vestibular injuries, the efficacy of therapeutic interventions are judged by a battery of functional assessments, including auditory brainstem response (ABR), distortion product otoacoustic emission (DPOAE) testing, vestibular sensory evoked potentials, and vestibulo-motor functional measurements. Mice that were exposed to blast shock waves of 19 pounds per square inch static pressure showed significant elevation of ABR threshold in wide-ranging acoustic frequency spectra and disappearance of DPOAE. Compared to low frequency (8 kilohertz) hearing, the impact to high frequency (40 kilohertz) hearing was severe. Those changes persisted through a month post-injury. Pathological evaluations by immunohistochemistry revealed a significant increase in the expression of GFAP and ionized calcium binding adaptor molecule 1 (Iba1) in the brainstem and cerebellum. Immunostaining of myosin VIIa (Myo7a) and Phalloidin in whole mount cochlea revealed appreciable damage to outer hair cells, inner hair cells, as well as to other structures in the inner ear. These data indicate that both peripheral and central auditory systems are vulnerable to blast injury and also point to neuroinflammation as a pivotal contributor to the secondary neuronal damage underlying these debilitating injuries. By revealing the neurobiological mechanisms that underlie BOP-induced auditory impairments and vestibular disruptions, these experiments will provide valuable insights into mitigation strategies and therapeutic countermeasures for affected Service Members.

### **Injury to the Retina and Brain Visual Centers by Primary Blast Waves**

Exposure to blast shock waves is a leading cause of loss of vision in military personnel. Blindness is a long-term disability that has a profound impact on the Service Member's QOL. Researchers at WRAIR, with support from VRP managed by CDMRP, have characterized the nature of blast wave injuries to the eyes (retina) and brain visual processing centers, and have explored therapies to halt the progression of neuronal cell degeneration.<sup>81</sup> Using a rat model of whole body exposure to BOP in a shock tube, visual function has been assessed by electroretinogram recordings, visual acuity testing (e.g., eye-tracking), and eye and brain histopathology. Exposure to moderate pressure blast waves (20 pounds per square inch peak amplitude, 6-8 millisecond duration) leads to marked visual system dysfunction that is associated with neuronal degeneration throughout the visual system (e.g., retina, optic tracts, and visual cortex). Novel drugs derived from n-3 and -6 PUFAs, which are known to be potent pro-resolving lipid mediators of inflammation (lipoxins, neuroprotectins, and resolvins), have been evaluated for therapeutic efficacy. Researchers have also looked at indirectly elevating these metabolites by giving the animals daily high dose n-3 fatty acid supplements (fish oil) prior to and post-injury. Despite subtle improvements in visual function, these treatments have not significantly impacted neuronal cell degeneration in the retina and brain or activation of immune cells involved in neuroinflammation processes (e.g., macrophage infiltration and cytokine release). One likely explanation for this lack of efficacy is that the pro-resolving lipid mediators of inflammation are not reaching presumed sites of action in adequate concentrations, prompting targeted drug delivery using nanoparticle platforms to eliminate drug stability and tissue permeability issues. By revealing the neurobiological mechanisms that

underlie BOP-induced ocular injury and vision impairments, these experiments will provide valuable insights into mitigation strategies and therapeutic countermeasures for affected Service Members.

## Treatment Strategies

### **Improving the Prognosis of Service Members with Acute Respiratory Distress Syndrome (ARDS) with Extracorporeal Gas Exchange (ECGE) Devices**

Combat explosions rose significantly, from 18 to 69 percent, between 2003 and 2005, resulting in an increased number of combat-related burn injuries.<sup>82</sup> Acute Lung Injury (ALI), and its most severe form, ARDS, often result from smoke inhalation, which is especially detrimental to those who suffer burn injuries. Patients who acquire ALI and ARDS from combat-related burns are characterized by the sudden onset of edema in the lungs, leading to decreased exchange of oxygen and carbon dioxide. Approximately 33 percent of mechanically ventilated Service Members with burn injuries develop ARDS, and this often prevents them from returning to duty.<sup>81,82</sup> Recent studies also indicate mortality rates significantly increase for burn victims whom develop ARDS.<sup>82</sup> Additionally, mortality rates were found to increase with ARDS severity with mild, moderate, and severe ARDS diagnoses accounting for mortality rates of 11.1, 36.1 and 43.8 percent, respectively.<sup>83</sup> The mortality rate for burn victims who do not develop ARDS was 8.7 percent.<sup>83</sup> Current treatment options for ALI and ARDS are limited to supportive care such as use of a mechanical ventilator, which exacerbates ALI and leads to multi-organ failure. Researchers at USAISR study and develop both non-invasive and invasive techniques to treat ARDS due to smoke inhalation, burns, and combined models of trauma. The team is carrying out a comprehensive benchmarking study of three minimally invasive ECGE devices: the Hemolung (Alung Technologies, USA), the

Mini Lung Petite System (Novalung, Xenios, Germany), and the Cardiohelp (Maquet Cardiopulmonary, USA). These miniaturized, self-operating, and portable ECGE devices are evaluated for therapeutic feasibility and improved outcomes in combat-burn patients. Using an animal model, the therapeutic efficacy of the ECGE devices is evaluated for their ability to lower injurious ventilator settings during transport and to reduce inflammatory responses, thereby preventing the onset of ARDS.

Preliminary data obtained in the first two years showed that all the devices enabled removal of nearly 50 percent of metabolically produced CO<sub>2</sub> and significant (from 25–50 percent) reduction in minute ventilation settings at blood flow rates ranging from only 500–800 milliliters per minute using 15-18 French scale catheters. This alone is an improvement over traditional methods of extracorporeal life support utilizing large catheters (27-32 French scale) that require blood flow rates of 2 to 5 liters per minute. Decreasing the high mechanical ventilator settings has a crucial effect on reducing ventilator-induced lung injury. Recently acquired benchmarking data suggests that the NovaLung Mini Lung Petite device is the most versatile and therapeutically efficient because it can be connected to oxygenators of various sizes (pediatric to large size) – all within the same system which can address ARDS of varying severity.

These studies are expected to lead to novel and improved CPGs for use of ECGE devices which could reduce ventilator-induced lung injury, and more importantly could reduce inflammatory responses and thereby potentially prevent the onset of ARDS.

### **Defective Methionine Metabolism in the Brain after Repeated Blast Exposures Might Contribute to Increased Oxidative Stress**

Increased oxidative stress in the brain is



reported to play a significant role promoting neuronal damage associated with both brain injury and neurodegenerative disorders. The mechanisms leading to increased oxidative stress after blast exposure are still uncertain. Researchers at the WRAIR explored the mechanisms underlying this increase in oxidative stress using preclinical models of repeated blast-induced TBI. In this study, brain regions of rats exposed to repeated blasts in a blast simulator underwent untargeted profiling of primary metabolism by automatic linear exchange/cold injection gas chromatography - time of flight mass spectrometry and revealed acute and chronic disruptions in the metabolism of amino acids and antioxidants. Closely coupled repeated blast exposures (19 pounds per square inch peak total pressure, 8 millisecond duration) affected the metabolism of the essential amino acid methionine. Methionine sulfoxide, the oxidized metabolite of methionine, showed a sustained increase in the brain after blast exposure which was associated with a significant decrease in cysteine, the amino acid derived from methionine. Glutathione, the antioxidant synthesized from cysteine, similarly decreased as did the antioxidant ascorbic acid. Reductions in ascorbic acid were accompanied by increased levels of its oxidized metabolite, dehydroascorbic acid and other metabolites such as threonic acid, isothreonic acid, glycolic acid, and oxalic acid. In view of the fundamental importance of glutathione in the brain as an antioxidant, including its role in the reduction of dehydroascorbic acid to ascorbic acid, the disruptions in methionine metabolism elicited by blast exposure might prominently contribute to neuronal injury by promoting increased and sustained oxidative stress. These results suggest that increasing the levels of cysteine in the brain by dietary supplementation of cysteine or administration of N-acetyl cysteine could be potential

therapeutic strategies against blast-induced TBI. By revealing important neurobiological mechanisms that underlie BOP-induced brain injury, these experiments will provide valuable insights into mitigation strategies and therapeutic countermeasures for affected Service Members.

### **Nose-to-Brain Delivery of Therapeutic Agents against Blast-induced TBI**

Several neuroprotective compounds showing efficacy against neuronal injury in in vitro or ex vivo studies are limited for clinical applications due to their inability to cross the BBB. Non-invasive intranasal nose-to-brain delivery bypasses the BBB to rapidly deliver drugs to the CNS along the olfactory and trigeminal neural pathways. Studies conducted in various laboratories have shown that drugs applied in this manner can be detected in the brain and CSF within five-10 minutes of application. Charged molecules, neuroactive peptides, and small proteins which cannot permeate the BBB can be rapidly delivered to the brain in minutes through the nasal route. The non-invasive intranasal administration doesn't require sterile conditions and hence can be self-administered in non-sterile environments such as on the battlefield. Since intranasally administered drugs avoid hepatic first-pass effect and subsequent dilution, it will be very cost effective. Using validated pre-clinical rodent models of single and repeated blast-induced TBI utilizing an ABS, researchers at WRAIR have demonstrated quantitative intranasal delivery to the brain of polar macromolecules otherwise excluded by the BBB and are evaluating the efficacy of these molecules as countermeasures to blast-induced neurotrauma following this novel route of administration. The intranasal brain delivery of drugs is being evaluated using the Precision Olfactory Delivery (POD) device from Impel NeuroPharma obtained using a

Material Transfer Agreement. Preliminary data collected from this study showed that N-acetyl cysteine and N-acetyl tryptophan, two potential neuroprotective drugs which cannot easily penetrate the BBB, can be delivered to the brain in significant amounts using the POD in rats. By establishing an effective delivery route of efficacious agents to the injured brain that are otherwise excluded by the BBB, these experiments will expand the realm and provide valuable insights into intranasal brain delivery of therapeutic countermeasures for affected Service Members.

### **Operation Brain Trauma Therapy (OBTT)-Extended Studies**

OBTT (<http://safar.pitt.edu/obtt>) is a consortium of top experimental TBI centers in the world to rapidly screen potential TBI therapies and evaluate TBI biomarkers in preclinical experimental models and translate them ultimately for use in combat casualty care. Member institutions include military and civilian academic centers in partnership with industry. This group brings together unprecedented expertise in experimental TBI research including all of the necessary tools for preclinical drug screening and biomarker development. OBTT uses a two-tier screening process to rapidly evaluate potential new drugs. In Tier A, OBTT uses established models of TBI in rats to screen the potential new therapies, using a standard battery of tests. Those agents that perform well advance to Tier B, in which more advanced tests are performed in rat models of TBI. In each tier, biomarkers of TBI are also evaluated. The most promising agent each year from Tier B advances to secondary screening in models of TBI in micropigs. To date, OBTT has tested nine therapies across three rodent models, with over 5,000 individual biomarker assessments. Two of these potential new drugs, levetiracetam and glibenclamide, have shown promising effects in one or more of the

TBI rat models. Levetiracetam was identified as the most promising therapy to date, and was advanced to testing in micropigs. Glibenclamide has shown promise specifically in contusions and might represent an excellent candidate for a precision medicine approach to treating cerebral contusions. In addition, data from rigorous preclinical testing across three experimental models on two biomarkers, GFAP and ubiquitin carboxy-terminal hydrolase L1, were very favorably reviewed by the FDA in the applications for ultimate clinical use of these markers as TBI drug development tools. Finally, promising data are being observed by OBTT in exploratory studies with the more novel serum biomarker phospho-neurofilament-heavy.

OBTT's efforts have garnered national and international acclaim and exposure. In March 2016, a total of seven manuscripts<sup>84-90</sup> were published together as a special issue of the *Journal of Neurotrauma* describing the results of the first five therapies tested by OBTT with an introduction by the Director of the CCCRP and Neurotrauma Portfolio Manager.<sup>91</sup> The current lack of an effective therapy for TBI is a critical problem facing Service Members, and the work of OBTT in developing new treatment options is of considerable importance for those who are injured. Agents tested have favorable safety profiles and most have been used clinically; therefore, a seamless transition to human clinical trials is anticipated.

### **Functional and Structural Changes in Cerebral Vasculature Following Exposure to Blast**

TBI is a leading contributor to combat related injury and death. Casualties from OIF and OEF have drawn increased attention to this injury. The subset of TBI cases due to blast injury present a particularly prominent and difficult problem. Explosion or blast is the most common cause of war injuries in OEF/OIF and the proliferation of IEDs has dramatically increased the numbers of

BOP-induced TBI observed on the battlefield. Moreover, exposure to multiple low intensity blast events with or without overt concussion has an additive effect with long-term neurologic and other health consequences. A prominent neurological complication associated with severe blast-induced TBI in casualties from OIF and OEF was significant cerebral vasospasm. Despite clinical indications of vascular insult and supporting experimental data in animals, there remains a paucity of information on specific structural and functional changes in the cerebral vascular space that occur after blast exposure. To further understand this complication, researchers at NMRC are evaluating alterations within the cerebral vasculature in a rat model of blast-induced TBI. The studies being conducted use an established rodent model to assess the effects of a single exposure to varying BOP intensities on cerebral macro- and micro-vasculature up to six months after exposure with an emphasis on identifying physiological underpinnings associated with cerebral vasospasm. Study techniques include functional indices of vascular function using intravital microscopy to assess changes within the cerebrovascular responsiveness after exposure to BOP. Structural assessment is being accomplished using electron microscopy coupled with immunostaining techniques to visualize changes to vascular endothelium, including the glycocalyx, assessment of tight junctions, perivascular edema, and changes in endothelin-1 within the vasculature. Initial results show that blast-exposed rats demonstrate cerebrovascular weakening, reduction of the endothelial glycocalyx structure in cerebral vessels, and blunting of induced vasoconstriction in cerebral arteries. Results also suggest that functional changes in cerebrovascular responses after blast occur in a time-dependent manner. Additional studies will be conducted to assess the effects of single and multiple exposures to varying BOP intensities on

cerebral macro- and micro-vasculature up to six months after exposure. Characterization of cerebrovascular reactivity after blast-induced TBI is critical to our understanding of vascular pathology in blast-exposed military personnel. It is important for developing potential treatment strategies for neurological symptoms in Service Members exposed to blast.

#### **Assessment of Cytokine Levels in Plasma, Brain, and Retina of a Rat Model of Blast-induced mTBI, Using Immunoassay Arrays**

Chemokines and cytokines play early pivotal roles in the inflammatory cascades underlying blast-induced injuries and are promising targets for therapeutic interventions. To effectively pursue this therapeutic avenue, the timing of the interplay among these responses must be characterized to identify the key participants and the optimal therapeutic windows for intervention. Cytokine levels in plasma, brain, and retina are being longitudinally screened at varied times after blast exposure using immunoassay arrays based on newly developed Luminex® bead technology. The arrays (R&D Systems Inc.) are used to precisely simultaneously quantify very small concentrations (pico-molar) of up to 17 rat specific cytokines across a single 96 sample well plate. Thus, this method is highly time and cost effective. Analyses to date of plasma and brains collected from blast-exposed rats reveal marked increases (> 2-fold) in the pro-inflammatory cytokines Chemokine (C-X-C motif) ligand 2 (CXCL2), CXCL3, intercellular adhesion molecule 1, interleukin 1 alpha (IL-1 $\alpha$ ), IL-6, and tumor necrosis factor alpha along with elevations in the inflammation resolving cytokines IL-4 and tissue inhibitors of metalloproteinase 1 up to seven days post-insult. We have also shown using MRI (fluorine-19 (<sup>19</sup>F)-MRI) of an intravenously injected perfluorocarbon contrast agent which is readily taken up by macrophages that extensive immune cell infiltration occurs

within the brain and retina by three days post-exposure. These findings have been corroborated by immunohistochemistry of brain and eye sections using biomarkers for activated immune cells, (e.g., Iba1 and cluster of differentiation 68 (CD68)). Cytokines can act as recruitment factors for macrophages into tissues, and in turn are excreted by these immune cells as signaling molecules that further trigger protein-pathways involved in apoptosis of neurons, (e.g., caspases). Based upon these response profiles, interventions with existing compounds targeting these mediators are likely to be most effective during subacute or acute phases of injury. By revealing the neurobiological mechanisms that underlie BOP-induced TBI, these experiments will provide valuable insights into mitigation strategies and therapeutic countermeasures for affected Service Members.

#### **Anti-Lysophosphatidic Acid (LPA) Antibody Treatment for Protection against Blast-induced Neurotrauma and Ocular Injuries**

BOP exposure leads to severity-dependent brain injury. LPA is a bioactive lysophospholipid released from activated platelets, astrocytes, choroidal plexus cells, and microglia and is reported to play major roles in promoting inflammatory processes through signaling events mediated through specific G-protein coupled LPA receptors (LPARs). In particular, LPA is reported to be involved in BBB disruption, Tau protein phosphorylation, and neuroinflammation leading to neurite retraction. Recent reports have noted elevated LPA and up-regulation of LPARs in both mice and humans following brain injury, and the neuroprotective efficacy of LPA antibodies (Lpathomab) in the rodent models. Researchers at WRAIR, in collaboration with Lpath, Inc. (the developer of Lpathomab), are evaluating the role of LPA in ameliorating the deleterious effects of blast-induced neurotrauma and ocular

injuries. Rats were exposed to single BOP using an ABS and given one intraperitoneal injection of anti-LPA antibody (25 milligrams per kilogram body weight) at one hour post-blast. Researchers determined retinal pathology on days one and 15 post-blast using H&E staining and ocular function on days two and six post-blast using a visual acuity test. Findings to date reveal that anti-LPA antibody treatment significantly reduced retinal neuropathological changes and improved visual acuity in rats after blast exposure, reinforcing previous indications that therapies targeting LPA may provide effective countermeasures to blast injury. By revealing the neurobiological mechanisms that underlie BOP-induced ocular injury and vision impairments, these experiments will provide valuable insights into mitigation strategies and therapeutic countermeasures for affected Service Members.

#### **Damage Control Ophthalmology (DCO) Initiative**

The DCO Initiative is an effort lead by researchers at VCE to collate essential management principles of urgent ocular trauma care to be used by deployed ophthalmologists. Currently, no such resource is available to deployed clinicians. A primary focus of the DCO Initiative is to determine the best management practices of acute mass casualties and complex ocular polytrauma that are often associated with blast-related injuries. VCE is presently gathering input from tri-service combat trauma experts as well as representatives from federal, civilian, and academic organizations. In order to collect input from leading experts, VCE hosted working groups at the American Academy of Ophthalmology's Annual Scientific Symposium (November 2015), the USUHS Annual Tri-Service Ocular Trauma Course (May 2016) and the Tri-Service Refractive Surgery Safety and Standards Symposium (June 2016). The outcome of



this initiative will be recommendations for the clinical management of acute, complex combat eye injuries, including blast-related injuries. While the initiative was primarily designed for the military ophthalmologist, the concept has garnered the attention of the civilian ophthalmic community and the American Academy of Ophthalmology due to the translatability of these findings across ophthalmology communities.

#### **Worldwide Ocular Trauma Teleconference**

VCE initiated and continues to host the Worldwide Ocular Trauma Teleconference which is a monthly teleconference attended by DoD, VA, and civilian academic clinical providers, as well as systems-level organizations influencing combat casualty care and policy to provide clinical follow-up of ocular casualties as well as identify local- and systems-level shortfalls and successes. This teleconference facilitates clinical follow-up of ocular casualties across the continuum of care and provides an active clinical feedback forum between deployed ophthalmologists and colleagues stateside. The forum also provides clinical continuity to the ever-rotating deployed providers, acts as a platform for discussing and elaborating DCO principles, and provides continuing medical education-accredited credit on the management of ocular trauma.

#### **VCE-Joint Pathology Center Fact Sheet**

Embedded foreign bodies in and around the eye and orbit are common sequelae of the modern battlefield, particularly with respect to blast injuries. The composition of those retained foreign bodies, particularly if iron or copper, can affect treatment and visual outcomes. Until recently, no pathway existed for providing such a compositional analysis. Researchers at VCE in collaboration with the DoD Joint Pathology Center developed a multi-service/multi-organizationally vetted

pathway for sophisticated compositional analysis of orbital, peri-orbital, and intraocular foreign bodies. This pathway addresses the recognized clinical gap in addition to bringing ocular foreign body management in line with ASD(HA) Policy Memorandum 07-029 “Policy on Analysis of Metal Fragments Removed from Department of Defense Personnel.”<sup>92</sup> While specifically aimed at DoD ophthalmic providers, the service is available to VA facilities as well, though interagency fees may apply. The pathway is currently presented as a joint VCE-Joint Pathology Center Fact Sheet and is being distributed.

#### **Mesenchymal Progenitor Cell Therapy to Prevent Muscle Fibrosis**

Recent military conflicts in Iraq and Afghanistan (OIF and OEF) have resulted in a number of military casualties with a disproportionately large number of orthopedic injuries. These traumatic extremity injuries are in many ways unique when compared to their civilian equivalents because of the associated tissue loss and dysfunction. In the scenario of devastating tissue destruction, the body’s first response is to heal itself and repair or regenerate damaged or missing tissue. The repair process tries to prepare the microenvironment for the creation of a functional tissue. However, if the microenvironment is not biologically favorable for functional tissue creation, then a non-functional, tissue-void filler is produced (known as scar tissue) and the tissue repair mechanisms are attenuated. Once the microenvironment changes from one of wound healing (tissue repair and regeneration) to that of wound closure (scar formation) the previously biologically active wound bed becomes less active and the scar tissue actively contracts in an effort to close the wound.

This study was funded by the DMRDP, managed by CDMRP, and conducted at NICoE. Tissue samples were obtained from Service

Members who have been wounded in combat and are undergoing surgical debridement at WRNMMC. The purpose of this study was to demonstrate that mesenchymal progenitor cells (MPCs)/trauma induced stem cells isolated from war-time extremity injuries are similar to mesenchymal stem cells (MSCs). One notable and significant advantage of MPCs is that the MPC population found in traumatic wounds is approximately 10,000 times more plentiful than the MSC population found in bone marrow. Using the clinical samples collected from WRNMMC, the study team has established the optimized parameters for the MPC/trauma induced stem cell harvesting procedure and completed a safety analysis of the harvesting method that can be used as justification for a future Phase 2 clinical trial. In addition, using an in vivo rat model, the effectiveness of MPC/trauma induced stem cell therapy to prevent dysregulated healing, exuberant scar formation, and muscle fibrosis and contracture following traumatic injury has been demonstrated.

Wartime traumatic extremity injuries are in many ways unique when compared to civilian equivalents because of the associated tremendous tissue loss and dysfunction. Often times the tissue is damaged beyond repair or involves a significant segmental defect rendering it non-functional. After thorough surgical debridements, the critical decision of whether to pursue limb salvage versus amputation needs to be made. The significant increase in availability of MPCs make them a practical choice for tissue engineering and regenerative medicine applications, especially if harvested in the same surgical setting that a reconstructive procedure will be performed. It is believed that these cells are central to tissue repair and regeneration and have the potential to augment wound healing through contributing to functional tissue repair. The knowledge gained from these experiments will

lead to novel cellular therapies that are feasible for military medical centers. Our strategy has the potential to improve the outcome of wounded Service Members resulting in an increased return to service rate, improvement in active duty retention rate, and reduction in long-term disability rates.

## Wound Infection

### **Antibiotic-loaded Biopolymer Sponge for Prevention of Polymicrobial Wound Infection**

In the field, musculoskeletal injury, from blast exposure or otherwise, often causes large wounds that are susceptible to infection by multiple microbes and/or biofilm formation. These infections are difficult to treat, particularly in theater with limited medical resources. Under a grant from the DMRDP managed by CDMRP, researchers from the University of Memphis have created a customizable, dual antibiotic-loaded chitosan sponge delivery system to provide reliable, low-cost infection prevention that can be used in conjunction with surgical debridement and irrigation. The study team previously provided data to show the effectiveness of the sponge against polymicrobial bacterial infections in animal models, and their commercial licensing partner Bionova Medical Inc. has since commercialized and launched the chitosan technology as the Sentrex BioSponge™.<sup>93</sup> To date, the Sentrex BioSponge™, which was added to the Federal Supply Schedule in 2015, has been used in more than 30 facilities in over 1,500 cases, including applications in orthopedic trauma, diabetic foot ulcers, sternal wounds, chronic venous ulcers, spinal hardware revisions, foot and ankle procedures, upper extremity injuries, abdominal injuries, and amputation sites. Additionally in 2016, the study team provided evidence that the chitosan sponge system can also prevent bacterial contamination of or around the

bone and fixation pin when higher antibiotic dosages are used.<sup>94</sup> The effectiveness of the sponge in removing and preventing biofilm formation was tested in an established mouse model. Although the sponge technology is not effective against established mature biofilm infections, data from the team's complex extremity model and infected fixation model show effectiveness in preventing infections in polymicrobial contaminated wounds with and without hardware. The Sentrex BioSponge™ has already improved treatment outcomes for extremity fractures in military patients. The customizable aspect of this innovative technology has and will continue to lend itself to many applications of wound healing, and infection prevention and control in the military environment.

#### **Blast-related Polytraumatic Extremity Wounds and Infectious Outcomes: Trauma Infectious Disease Outcomes Study (TIDOS)**

The DoD and VA Multicenter Cohort Study evaluating Infection-associated Clinical Outcomes in Hospitalized Medical Evacuees following Traumatic Injury (i.e., TIDOS) was initiated on FY09 with the following objectives: 1) Establish a cohort of DoD beneficiaries and active-duty personnel with trauma-related injuries to determine short- and long-term outcomes and potential risk factors associated with infections; 2) Describe the infectious disease epidemiology of trauma-related injuries or other nosocomial infections in the cohort population; 3) Establish a database and bacterial/fungal isolate repository to support future approved sub-studies focused on informing clinical management, disease prevention, or clinical trial design; and 4) Inform DoD efforts to develop real-time tools for combat-related health event/outcome analysis secondary to trauma-related infections during wartime.

The TIDOS project is overseen by the

Infectious Disease Clinical Research Program (IDCRP) through USUHS. It is a collaborative project that involves investigators from a variety of disciplines (e.g., infectious disease, trauma surgery, orthopedics, epidemiology, microbiology, pathology, statistics, and molecular biology) across multiple clinical sites, including USUHS, WRNMMC, San Antonio Military Medical Center, Landstuhl Regional Medical Center (LRMC), and the Saint Louis VA Medical Center. In addition, TIDOS also involves collaborations with investigators from USAISR, WRAIR, NMRC, and the United Kingdom Ministry of Defence Wound Infections Surveillance Programme.

The inclusion criteria for the TIDOS project included being an active duty personnel or DoD beneficiary, over 18 years of age, and sustaining a wound or injury during deployment requiring return via LRMC to a participating military hospital in the US. Patient trauma history, ISS, and surgical management was obtained for all military trauma patients (June 2009 through December 2014) through selected data elements retrieved from the DoD Trauma Registry (DoDTR). An infectious diseases module to augment the DoDTR was developed to capture infection-specific data throughout levels of care at participating hospitals. This infectious disease-specific information included diagnoses, treatments (antibiotic usage), and outcomes of bloodstream infections, clinical sepsis, bone and joint infections, skin and soft tissue infections, CNS infections, intra-thoracic/pulmonary infections, and intra-abdominal infection. Prior to hospital discharge, patients were given the opportunity to enroll in the longitudinal TIDOS cohort, which collected long-term infection-related information from patients at pre-determined intervals after hospital discharge (e.g., one month, three months, six months, 12 months, 18 months, and 24 months and then yearly). Information on infectious disease events related to the initial

trauma was collected through in-person and telephonic interviews, interaction with health providers, medical record review, and query of electronic healthcare databases. Enrolled patients who entered VA care were also given the opportunity to consent to data abstraction through review of the VA's Compensation and Pension Records Interchange.

Overall, the TIDOS project is one of the largest cohorts of OIF/OEF trauma patients capturing information following injury with an extended follow-up duration, allowing for comprehensive assessment of the full impact of trauma-related infections on military personnel. While there are similarities with other populations, wounded military personnel examined in TIDOS sustained trauma with a greater severity than seen in civilian trauma. In particular, patients in TIDOS frequently sustained dismounted blast trauma, resulting in at least one traumatic amputation of a lower extremity, as well as other grievous injuries. The severity of these injuries and inclusive nature of TIDOS makes this cohort unique and of critical relevance to the MHS.

Data gathered through TIDOS was crucial when faced with the emergent outbreak of invasive fungal infections (IFIs) in 2009-10 among patients with blast trauma. Analysis of data obtained through TIDOS identified risk factors for the development of IFIs, assessed clinical outcomes and morbidity (e.g., time to wound closure and amputations/amputation revisions), examined diagnostic methods, and evaluated wound microbiology. These data supported the development (and refinement) of a CPG specific to IFI management.<sup>95</sup> Furthermore, as TIDOS collected data through multiple levels of care and maintains a microbiological repository of isolates, the potential transmission of healthcare-associated multidrug-resistant organisms, including ESKAPE pathogens (encompass the six pathogens with growing multidrug resistant virulence: *Enterococcus*

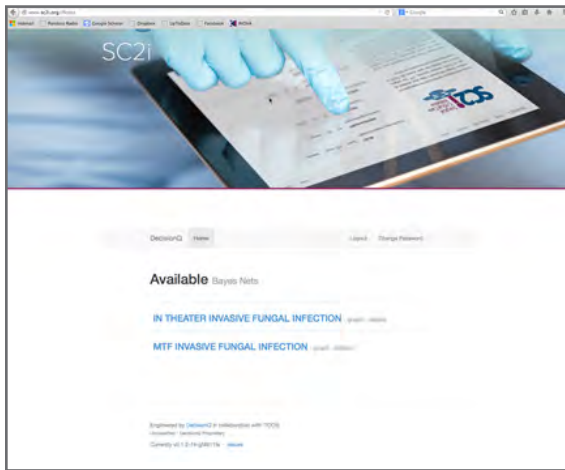
*faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter*, *Pseudomonas aeruginosa* and *Enterobacter*), is the focus of multiple investigations. Data collected through TIDOS also allowed for the development of CPGs and recommendations related to the prevention of combat trauma-related infections in these wounded Service Members.<sup>96</sup> Lastly, information collected through TIDOS is being utilized for the examination of antimicrobial practice patterns related to adherence to CGPs and potential improvements in antibiotic stewardship. In 2016, research conducted by TIDOS investigators has resulted in seven manuscripts in peer reviewed publications<sup>97-103</sup> and multiple abstract presentations at national and international meetings.<sup>104-106</sup>

The TIDOS project is supported by the US Navy BUMED WII Program, the National Institute of Allergy and Infectious Diseases (NIAID), the DoD Global Emerging Infections Surveillance and Response System, the MIDRP through the DHP, and US Army DMRDP.

### **Invasive Fungal Infection Clinical Decision Support**

In FY14, a CDST for IFIs was developed by researchers at SC2i at USUHS, and validated collaboratively with the IDCRP-TIDOS Group (Figure 7-19). This tool, designed to facilitate early diagnosis of patients with or at risk of IFI, enables early or prophylactic treatment with the aim of improving outcomes. Although they are usually uncommon, trauma-related IFIs in previously immuno-competent individuals are associated with considerable mortality (e.g., as high as 38 percent) and morbidity, often resulting in either permanent disability and/or extensive rehabilitation. The impact of IFI complications has also become increasingly relevant among wounded military personnel as advances in combat care during the recent conflicts in Iraq and Afghanistan improved the survivability of severe trauma, including blast-related traumatic amputations. The IFI





**FIGURE 7-19:** Invasive fungal wound infections CDST predicting risk for developing invasive fungal wound infections.

CDST will assist providers in controlling and preventing trauma-related IFIs in wounded Service Members. In FY16, the IFI CDST was completed and deployed for use by military surgeons to assess casualties within the Continental US and outside the Continental US. In addition, the use of the IFI CDST has been incorporated into the Joint Trauma System CPG for “Invasive Fungal Infection in War Wounds”.<sup>95</sup> As part of a process-improvement exercise, SC2i will monitor the use of the tool in FY17 and will provide improvements to the predictive model and user-interface as needed.

### **Biologically Active Advanced Antimicrobial Human Skin Substitute for the Treatment of Combat Wounds**

Combat-related trauma and blast injuries frequently result in skin loss and infection caused by contaminating foreign material in exposed wounds. Current skin substitutes on the market are designed to replace or compensate for nonfunctioning skin; however, none have been optimized to address the other major challenges in the management of traumatic wounds: direct reduction of microbial infection and enhancement of the immune response to combat the infection. Researchers from Stratatech Corporation (Madison, Wisconsin) have been conducting

preclinical studies that are focused on testing the ability of a novel antimicrobial skin tissue, ExpressGraft-C9T1, to promote wound healing and tissue restoration by the patient’s own skin and to prevent infection in combat-related wounds. ExpressGraft-C9T1 tissue is composed of a biodegradable matrix and human skin cells expressing the antimicrobial host defense peptide cathelicidin. The research team at Stratatech Corporation used animal models to show that their anti-infective skin replacement product was effective in the reduction of bacterial infection in wounds and remained non-toxic to the host animal. Data generated from this project supported an IND application to the FDA in April 2015, which enabled the May 2016 initiation of a Phase 2 clinical safety trial of the antimicrobial tissue in the treatment of skin wounds in humans (ClinicalTrials.gov Identifier: NCT02657876). In 2016, the project has focused on optimizing the anti-infective skin substitute for increased production and optimal shelf life for use in the aforementioned clinical trial and, potentially, for future commercialization. AFIRM has also funded further development of Stratatech Corporation’s first skin replacement product, called StrataGraft® tissue, with a now successfully completed Phase 2 clinical trial of StrataGraft® supporting use of this product to treat deep partial-thickness skin wounds. StrataGraft® has been determined to be Phase 3 ready by the FDA. If proven safe and effective, StrataGraft® skin tissue and ExpressGraft-C9T1 tissue could have a transformational effect on combat casualty care by advancing treatment of Service Members and Veterans recovering from combat-related wounds.

### **Program Area: Reset**

The DoD Blast Injury Research Program is committed to reducing recovery time and improving the QOL for Service Members who have experienced blast injuries. These efforts maximize the possibility of their RTD and reintegration into the civilian community and

workforce. Medical research in the area of Reset informs evidence-based clinical guidelines for procedures that restore critical function and improve disfigurement. It also forms the basis for rehabilitation programs for blast-related psychological disorders, amputations, and other injuries with long-term effects on QOL. Reset strategies backed by extensive medical research enable the DoD and military medical community to retain the confidence and trust of Service Members, their Families, and the American public through measureable improvements to Service Member recovery.

## Extremity Trauma Rehabilitation and Treatment

### **Promoting Adherence among Outpatients in Physical Rehabilitation Programs**

Researchers at the Center for Rehabilitation Sciences Research (CRSR) at USUHS conducted ethnographic interviews with former US Armed Forces Amputee Patient Care Program patients to understand their experiences when returning to duty and/or the civilian community following limb loss and/or limb salvage. The purpose of this ethnographic, or qualitative, study was to learn, using the concepts and frameworks of the research participants, about the experience of returning to life in the community after undergoing rehabilitative care for traumatic limb-loss. Thus far, researchers have learned that nearly all participants have attended some form of education or vocational retraining and have entered into the workforce; however, those who have not attended education or vocational retraining continue to confront health challenges associated with their injuries. In terms of personal relationships, nearly all participants report participating in, or having had, long-term relationships. Finally, Service Members noted that high technology prosthetics promoted confidence during rehabilitation and that focusing on athleticism during outpatient care prepared them to leave the program in excellent physical condition

making community living easier. Former patients also attributed working alongside similarly injured peers and having regular contact with their whole treatment team as the foundation of their self-described successes. By understanding the post-injury experiences of former Service Members, researchers are able to advise on how to refine rehabilitation programs to make them even more effective.

### **Optimization of Dynamic Ankle-foot Orthosis Design for High Level Activity Performance Following Limb Salvage for Severe Lower Extremity Trauma**

The Intrepid Dynamic Exoskeletal Orthosis (IDEO®) is a custom carbon fiber ankle-foot orthosis (AFO) that has helped wounded Service Members return to a highly active life following limb salvage after blast injuries. Its growing use within the Military prompted researchers to investigate how to better improve the customization process for patients. Researchers from EACE and BAMC utilizing funding from CRSR, in collaboration with the University of Texas, used 3D printing techniques and systematic modifications to IDEO® properties to better understand and optimize the design, manufacturing, and prescription process (Figure 7-20). Specifically, stiffness, bending axis, and alignment of the IDEO® were modified to determine their respective impacts on movement mechanics. Individuals who had undergone lower limb reconstruction and experienced plantar flexion weakness were recruited from the Center for the Intrepid (CFI) and underwent gait analysis during walking, running, and stair and ramp ascent/descent. Results demonstrated that participants adapted to a wide range in IDEO® stiffnesses with few deviations to joint mechanics and muscle activity, possibly reducing the burden on the orthotist to test numerous designs for an individual. When the bending axis of the IDEO® flexed low, near a biological ankle, there were few large

changes in walking gait, but greater range of motion and power during running: potentially a beneficial design feature for patients who can tolerate greater motion. The alignment of the IDEO® in a toe-down position was important for minimizing knee extensor muscle activity during a variety of activities, but it compromised push-off power during running. Patient preference across all three studies was generally mixed with no single design preferred by all users. The combined results indicate that a single design may not be optimal for all individuals or for all activities and stress the importance of considering the preference and functional goals of the patient. The work of this group has resulted in seven manuscripts accepted in peer reviewed publications<sup>107-113</sup> and two additional manuscripts currently under review. By evaluating the IDEO®'s design properties and investigating new manufacturing techniques, researchers can provide clinicians with important information regarding improvements in the device to aid the Service Member return to a highly active life after injury.

### Identifying Predictors of Osteoarthritis in Service Members with Unilateral Lower Extremity Amputations

Increased or abnormal loading on the intact limb contributes to the relatively high risk of knee osteoarthritis in individuals with unilateral lower limb loss. This abnormal loading may occur through various methods of locomotion, (e.g., walking and running), but one method, hopping, may be a unique form of locomotion for this population whose mechanical effects are unknown. Loading rates during single-limb hopping was assessed in healthy controls in a study conducted by researchers at EACE and CRSR researchers at WRNMMC.<sup>114</sup> Hopping loads were compared to loading rates and patterns of more common methods of locomotion, walking and running, to determine if this form may be contributing

to the higher rates of OA in the limb loss population. The findings demonstrated that kinetic measures at the knee joint are greater in hopping compared to walking. Therefore single-leg forward hopping should be limited, and alternatives such as the use of a crutch or wheelchair should be encouraged in the limb loss population until OA risk is fully understood. Understanding why individuals



**FIGURE 7-20: Top Image:** 3D printing methods (selective laser sintering) modified the stiffness of the IDEO®'s posterior strut.

**Middle Image:** High, mid, and low IDEO® bending axis locations were created using 3D printing techniques (selective laser sintering).

**Bottom Image:** IDEO® alignment was modified by placing a 3-degree wedge between the posterior strut and footplate

with lower limb loss develop knee OA in their uninjured limb at higher rates will allow for the development of medical interventions to reduce the factors that increase the risk.

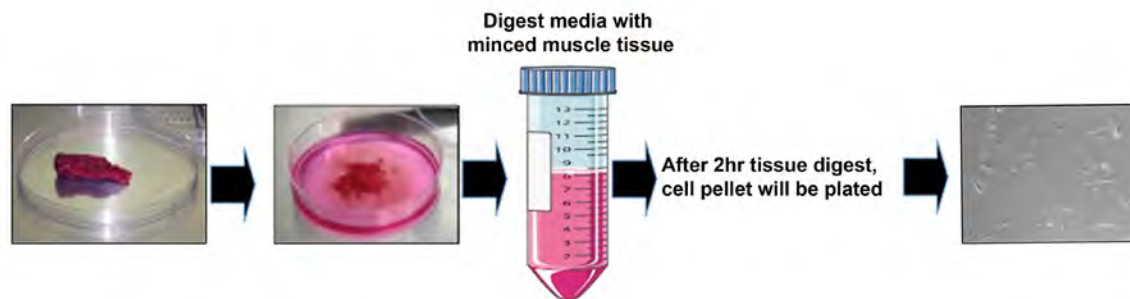
### **Stem Cell Based Neurotrophic Enhancement of an Aligned Nanofiber Scaffold for Nerve Repair**

Peripheral nerve trauma is a challenging complication of wartime injuries and often leads to significant disability and dysfunction. Current wartime combat operations have resulted in many injuries to Service Member's limbs as a result of explosive blasts. What many of these injuries have in common is that they significantly affect the peripheral nerves involved in these areas. Certain cells collected from traumatized muscle tissue were found to behave similarly to stem cells, normally found in bone marrow, which are known to help regenerate tissue by either direct differentiation or secreted trophic factors. These cells with tissue/bio-engineered microenvironment could become useful in treating injured Service Members suffering from peripheral nerve injuries by reinserting them back into the injured areas so that missing nerve connections can be regenerated and finally return to functional level recovery quickly. Researchers at USUHS are conducting a study to test the hypothesis that MPC derived from traumatized muscle and seeded within a biodegradable scaffold consisting of aligned nanofibers are capable of providing neurotrophic enhancement of nerve regeneration by generating a biochemical bridge that promotes axonal growth and migration of cells. This study is funded by the PRORP and managed by CDMRP. The study team identified a population of MPCs from war-traumatized muscle tissue (Figure 7-21). The morphology and cell surface epitope profiles of MPCs are similar to those of bone marrow-derived MSCs, which are the resident osteoprogenitor cells from the marrow stroma. Traumatized

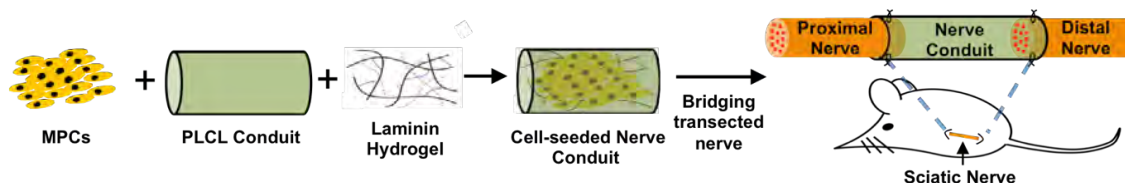
muscle-derived MPCs are also capable of giving rise to colony-forming-unit-fibroblasts, an indicator of a clonogenic, multipotent cell population. The MPCs appeared to be a distinct population of progenitor cells with characteristic similarities to bone marrow-derived MSCs, with some notable differences between the MPCs and MSCs, which likely reflect their different tissue of origin and in vivo function, and both cell types converge on the osteogenic differentiation pathway under appropriate induction. MPCs are also capable of differentiating into two other mesenchymal lineages, adipocytes and chondrocytes. In addition, they may also be useful in the development of tissue engineering strategies of regenerative medicine. In the first ten months of this project, researchers at USUHS have developed methods to fabricate a nanofiber-based scaffold with the appropriate geometry and have verified the alignment of the nanofibers along the longitudinal axis of the graft. In addition, the device has been optimized to have sufficient mechanical strength for surgical handling and suture retention. During this study, researchers seeded these grafts with the human MPCs in vitro, and evaluated the effect of the cell/scaffold composite on the cells responsible for nerve regeneration using rat sciatic nerve transection defect model of nerve injury (Figure 7-22). MPCs appear to be a promising cell type for cellular therapy to enhance tissue regeneration, and may be useful as an autologous cell type at the point-of-care. They express several factors that are known to enhance neuron function after injury and this research provides further evidence indicating that these cells may be useful to promote peripheral nerve regeneration. The MPCs appear to exhibit neurotrophic function when exposed to factors that are up regulated by nerve injury, suggesting that the MPCs may be induced to perform their neurotrophic function in situ. The research outcomes described demonstrates preliminary



**FIGURE 7-21:** Workflow how to isolate Mesenchymal Progenitor cells (MPCs) from trauma blast injured tissue.



**FIGURE 7-22:** Schematic of the prepared MPCs loaded nerve conduits and implantation in the rat sciatic nerve transection model.



evidence of human MPC enhancing nerve regeneration at the early time point (two-week) in a well-established rodent peripheral nerve transection model. The nature of the nerve growth and the neurotrophic activity of the MPC will be further elucidated upon completion of the ongoing research tasks.

### **Evaluation of Next Generation Regenerative Medicine Therapeutics and Approaches for the Restoration of Tissue Structure and Function Following Traumatic Injury**

War-related trauma often results in complex, composite tissue injuries which can result in persistent functional deficits, chronic disability, and reduced QOL. To address this unmet clinical need, the regenerative medicine field has made significant efforts in recent years toward the development of innovative short- and long-term solutions. A focus of EACE Medical/Surgical Interventions line of inquiry at WRNMMC and USUHS is the evaluation of next generation regenerative medicine therapeutics and approaches for the restoration of tissue structure and function following traumatic injury. This is particularly relevant for Service Members

and Veterans with extremity trauma and/or amputation. Three studies were published by EACE staff in this line of research:

The first study reports on the role of a biologic scaffold material, urinary bladder matrix (UBM), in wound care and reconstruction of traumatic and combat wounds.<sup>115</sup> The UBM, an acellular, non-cross-linked, resorbable, biologically-derived extracellular matrix scaffold, was found to facilitate definitive soft tissue reconstruction by establishing a neovascularized soft tissue base acceptable for second stage wound and skin coverage options within traumatic and combat-related wounds. This study demonstrates that the use of a regenerative medicine therapeutic in conjunction with other reconstructive techniques can be a successful adjunct in the reconstructive algorithm for complex traumatic wound reconstruction and limb salvage procedures.

The second study was undertaken to further understand the impact of the manufacturing process on the ability of a regenerative medicine technology to facilitate tissue reconstruction.<sup>116</sup> Specifically, the objective of this study was to elucidate the most effective yet minimally destructive

sterilization protocol for a biologic scaffold material. Three different sterilization methodologies - ethylene oxide, gamma irradiation, and electron beam irradiation – were evaluated for their effect on the material properties of a porcine dermal biologic scaffold and the elicited *in vivo* remodeling response. *In vitro* results show that increasing irradiation dosage resulted in a dose dependent decrease in mechanical properties compared to untreated controls. The study showed that increasing levels of irradiation induced an adverse effect on the material properties and augmented the remodeling response both *in vitro* and *in vivo*. These findings highlight the importance of selecting an appropriate type and dose of sterilization for biologic scaffold materials to optimize their material properties and performance *in vivo*.

The third study investigated the effect of aspirin on the ability of a biologic scaffold material to facilitate skeletal muscle tissue reconstruction following injury.<sup>117</sup> The findings suggest that aspirin can negatively impact the repair/regeneration events elicited by biologic scaffolds in a skeletal muscle injury model. Additional work must be conducted to determine if these deleterious effects of aspirin will irreparably reduce the regenerative response or simply delay it. The results of the current work not only provide a better understanding of the mechanisms involved in biologic scaffold mediated constructive remodeling and begin to classify molecular targets to be used as metrics for the development of next generation biologic scaffolds, but also substantiate the possibility that the use of non-steroidal anti-inflammatory drugs may significantly alter tissue remodeling outcomes in regenerative medicine/tissue engineering applications.

### **Novel Rehabilitation Strategies**

EACE continues to conduct investigations with resulting publications in the area

of perturbation-based gait training in a virtual environment. Roughly 50 percent of individuals with lower limb amputation report a fear of falling and fall at least once a year. Perturbation-based gait training in a challenging simulated environment shows promise for improving walking stability and incorporation into a rehabilitation program. Perturbation-based gait training and the use of virtual environments have been shown independently to be effective at improving walking stability in patient populations. An intervention was developed combining the strengths of the two paradigms utilizing continuous, walking surface angle oscillations within a virtual environment. One published case report describes walking function and mediolateral stability outcomes of an individual with a unilateral transfemoral amputation following a novel perturbation-based gait training intervention in a virtual environment.<sup>118</sup> Perturbation-based gait training in a challenging simulated environment shows promise for improving walking stability and incorporation into a rehabilitation program. This intervention has been implemented clinically, and researchers are exploring additional uses of virtual reality to challenge and assess stability. An additional study systematically determined the between-session reliability and minimum detectable change values of temporal-spatial, kinematic variability, and dynamic stability measures during three types of perturbed gait.<sup>119</sup> Twenty young healthy adults completed two identical testing sessions two weeks apart, comprised of an unperturbed and three perturbed (cognitive, physical, and visual) walking conditions in a virtual reality environment. Temporal-spatial, kinematic variability, and dynamic stability measures collected during perturbation-based assessment paradigms are often used to identify dysfunction associated with gait instability. However, it remains unclear which measures are most reliable for detecting and

tracking responses to perturbations. This study found that across all perturbation types, temporal-spatial, orbital and local measures were the most reliable measures with the lowest minimum detectable change values, supporting their use for tracking changes over multiple testing sessions. This intervention has been implemented clinically and researchers are exploring additional uses of virtual reality to challenge and assess stability (Figure 7-23 and Figure 7-24).

### **Advanced Prosthetics and Orthotics**

EACE researchers published results on the effects of AFO design on stair climbing mechanics.<sup>107</sup> The study examined both stair ascent and descent for IDEO® users and able bodied control participants. Reduced ankle range of motion and power on the IDEO® limb resulted in compensatory strategies to include greater bilateral hip power during stair ascent and large vertical ground reaction forces, and ankle and knee power absorption on the sound limb during descent. Studies such as this are important to improve the design and function of AFOs as well as contributing to the body of research to support clinical use and prescriptive criteria of specific orthotic devices. Another EACE study evaluated how experienced prosthesis users descended a slope using either an X2® or conventional knee (either mechanical or microprocessor).<sup>120</sup> Gait was more symmetrical and generally improved when wearing the X2® knee compared to a conventional knee and handrails were used less frequently. These findings suggest greater confidence in balance and walking abilities in the X2® prosthesis and contribute to the evidence to support clinical prescription. The ability to navigate stairs step-over-step is an important functional outcome following severe lower leg injury and is difficult for many patients. Despite gait deviations, IDEO® users were able to climb stairs step-over-step unassisted. Both of the studies contribute to evidence supporting

clinical prescription of advanced prosthetic and orthotic devices.

### **Utilizing Vascularized Bone to Improve Outcomes of Face Transplantation**

Severe craniofacial injuries are difficult reconstructive challenges and pose significant functional limitations such as difficulty with speech, oral competence, and facial expression for injured Service Members. Conventional methods of reconstructive surgery are often not sufficient to restore normal tissue function or aesthetics, and the need for lifelong immunosuppression to prevent rejection can lead to adverse effects. With support from the CRMRP and Reconstructive Transplant Research Programs, researchers from the New York University School of Medicine plan to investigate whether the inclusion of vascularized bone marrow in craniofacial allografts can minimize immunosuppression and improve functional and aesthetic outcomes in individuals who have sustained severe facial wounds. The initial research has focused on a novel paradigm in surgical technology to facilitate precision during two major phases of a VCA procedure – recipient preparation and donor procurement.<sup>121-123</sup> A systematic approach was established wherein craniofacial skeletons of donor and recipient cadavers were rendered in a 3-D virtual environment and then used to simulate a surgical plan and design donor- and recipient- specific surgical tools for precisely matching osteotomy paths. The personalized surgical tools were then fabricated by rapid prototyping, used to simulate craniofacial transplantations with the donor and recipient cadavers, and compared to cadaver transplantations performed with conventional surgery techniques. The use of virtual surgical planning and personalized surgical tools was shown to reduce the time required for donor procurement, recipient preparation, transplantation of the donor allograft, and the total operative time to complete the transplant, by 49-60 percent. A measurement tool to



**FIGURE 7-23:** Individual with a transfemoral amputation participating in a perturbation-based, gait training protocol within the virtual reality environment at Brooke Army Medical Center's Center for the Intrepid. Picture courtesy of Dr. Riley C. Sheehan.



**FIGURE 7-24:** Individual utilizing the Intrepid Dynamic Exoskeletal Orthosis, following limb trauma, to complete a simulated combat patrol task within the virtual reality environment at Brooke Army Medical Center's Center for the Intrepid. Picture courtesy of Dr. Christopher A. Rábago.

determine the accuracy of spatial positioning and bony contact was developed using the same virtual planning technology, and revealed that a personalized surgical approach significantly improved the placement of bony allografts in cadaver simulations. This research is expected to benefit Service Members and others with

devastating craniofacial injuries by providing a standardized and custom VCA surgical process which is defined by both the donor and recipient anatomies. This personalized approach will provide an optimal basis for a future clinical trial in which patients will receive a craniofacial transplant containing



a significant amount of vascularized bone marrow, which may be a promising approach to reducing lifelong immunosuppression and restoring normal facial function and appearance post-transplant.

### **A Graft-embedded Loco-regional Immunosuppressive Therapy Platform for VCA**

Surgical reconstruction by VCA offers life-enhancing benefits for Service Members who have sustained devastating injuries, such as loss of the hands. Wider clinical acceptance of VCA has been hampered by the requirement for lifelong and systemic immunosuppression, which has significant drawbacks including organ toxicity and risk of graft attrition upon medication non-compliance. Unlike the transplantation of solid organs, VCA offers a unique opportunity for graft access wherein immunosuppression can be administered directly to VCA tissues through targeted therapeutic technologies. Supported by the CRMRP and Reconstructive Transplant Research Programs, researchers from USAISR, Brigham and Women's Hospital, University of Pittsburgh, and the Institute for Stem Cell Biology and Regenerative Medicine have collaborated to develop a graft embedded, loco-regional immunosuppressive therapy (GEL-IT<sup>®</sup>) platform (Figure 7-25). In initial studies, an approach was established wherein the immunosuppressive drugs tacrolimus and rapamycin were encapsulated within amphiphilic triglycerol monostearate gels through self-assembly. A key feature of the hydrogel design is a nanofibrous matrix which degrades when proteolytic enzyme mediators of inflammation and allograft rejection are present in the biological milieu, thereby increasing the bioavailability of immunosuppressive drugs in relevant tissues. In vitro studies implementing an inflammatory-like state confirmed that the release of the encapsulated immunosuppressive drugs occurs primarily

in the presence of a proteolytic enzyme. An injectable formulation of the GEL-IT<sup>®</sup> hydrogels was then tested in small animal models of syngeneic and allogeneic hind limb transplantation. Results of the study showed that a single administration of GEL-IT<sup>®</sup> hydrogels laden with tacrolimus alone or in combination with rapamycin prolonged graft survival for more than 60 days post-transplant, whereas Grade 3 rejection was detected approximately 21 days post-transplant in animals treated with rapamycin-containing hydrogels alone. Analysis of blood and tissue samples demonstrated that the level of drug released in vivo was proportional to the degree of inflammation, with initial burst release followed by drug concentrations maintained in a therapeutic range with minimal systemic exposure. The GEL-IT<sup>®</sup> platform is a novel approach to reducing the overall dosing, frequency, and duration of systemic immunosuppression required for allograft survival following VCA. This localized and self-titrating immunomodulation system will also obviate the risk of medication non-adherence and graft attrition resulting from uncontrolled rejection. Overall, the GEL-IT<sup>®</sup> platform is expected to benefit wounded Service Members by offering an optimized immunomodulation approach with lower risk of morbidity to enhance QOL and facilitate rehabilitation outcomes following VCA.

## **Health Outcomes Following Extremity Trauma**

### **Establishing the Mineral Apposition Rate of HO**

HO is a debilitating condition that occurs following traumatic injury and may restrict the range of motion and delay rehabilitation. The timing and efficacy of surgical resection have varied widely, and there is a gap in knowledge between clinical predictors of HO recurrence and histological analysis. Current timing of surgical interventions can prevent incidence of the development of HO which

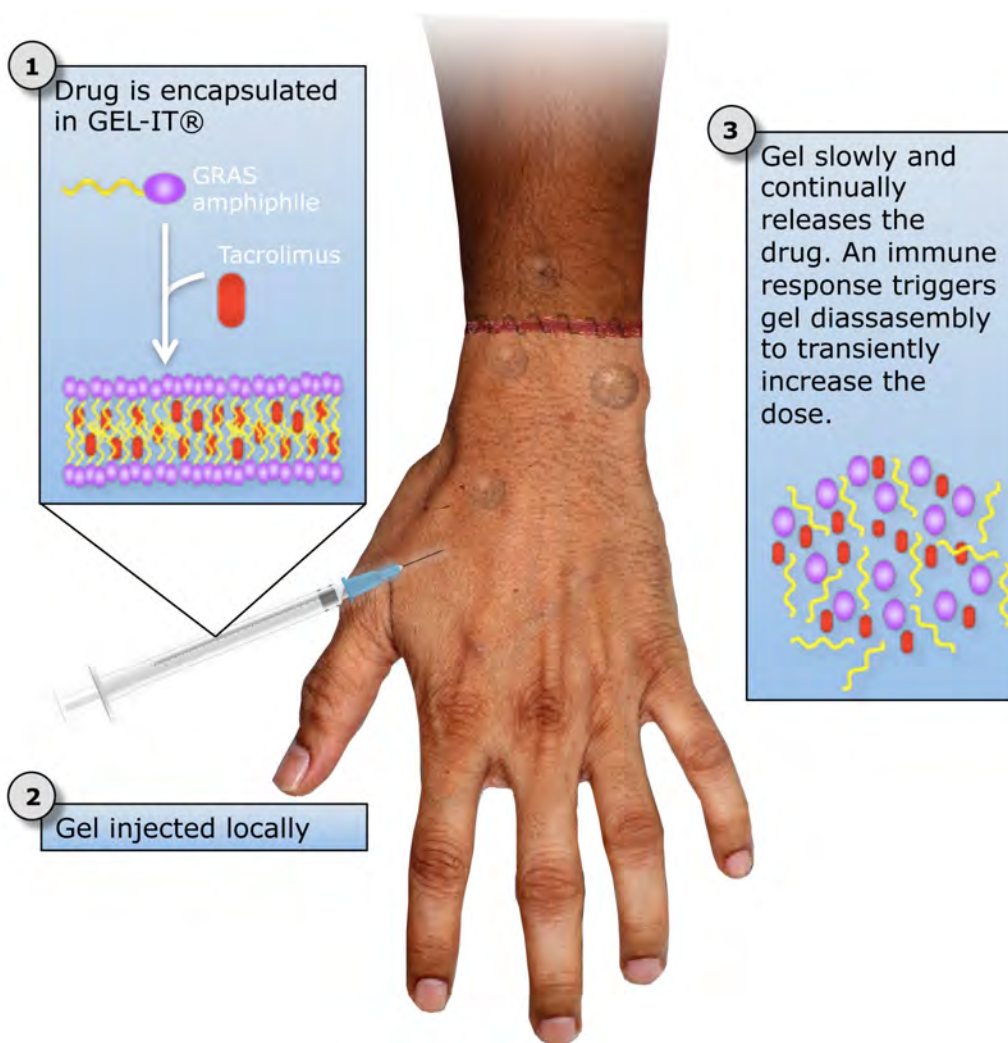
restricts joint movement in post-trauma patients. Data from CRSR has demonstrated a link between benchtop research and bedside care, with the mineral apposition rate elevated in patients with HO and correlated with recurrence severity.<sup>124,125</sup> Many of the Service Members who have sustained blast injuries have complications with HO, which causes pain via skin pressure and ulceration, associated inflammation, limitations of joint motion, and neurovascular entrapment. Resection of symptomatic HO and recurrence in injured Service Members has remained a challenging problem given the high potential

for comorbidities and severity of the injuries sustained. As a result, poor prosthetic fit may occur and delay the rehabilitation for Service Members who require socket adjustments to compensate for HO formation. Understanding the etiology of HO will lead to improved care management and may minimize the number of surgeries required to excise these masses.

### Comparison of 3-D Gait Analysis Data across DoD Sites

EACE researchers at the Advanced Rehabilitation Centers (WRNMMC, CFI, and NMCSD) contributed to a study to evaluate the

**FIGURE 7-25:** Encapsulation of tacrolimus in smart hydrogels and enzyme-triggered, on-cue drug release. Illustration courtesy of University of Pittsburgh, Brigham and Women’s Hospital and Institute for Stem Cell Biology and Regenerative Medicine collaborators: VS Gorantla, J Karp, N Joshi, P Vemula, AA Dhayani, A Fries, S Lawson, and MR Davis.



ability to collect and analyze the repeatability of kinematic and kinetic gait analysis data across the three sites. Data reliability is of utmost importance when attempting to share data across sites to evaluate patient progress or to pool research data for comparative effectiveness studies. Measurement consistency across sites participating in multi-center research studies directly influences required sample size, level of detectable difference, statistical power, and ultimately, the ability to detect real change. The same ten subjects were studied in all three laboratories, and data were collected over multiple trials across multiple sessions. Data were processed in each laboratory and then sent to an unbiased third party and analyzed. Data demonstrate that kinematic differences were less than 5.0 degrees for all joint angle measurements. However kinetic errors differed, but were greatly reduced when the subjects walked at their controlled speed.<sup>126</sup> This study, funded by CRSR, demonstrates that it is possible to obtain high quality, reliable data across multiple gait laboratories particularly when gait speed is standardized across testing sessions. These data open the door for sharing data across the sites for multi-center research studies and for patient care. It is possible to standardize the DCoE facilities to ensure Service Members receive the same consistent quality of care.

### **Characterization and Comparison of Combat-related Injuries in Women during OIF and OEF**

With the elimination of the direct combat exclusion rule for women, mission responsibilities will continue to change, bringing increased physical and mental risks to female Service Members as they take on more combat assignments. By studying gender differences that may exist in battle-injured Service Members, military leaders and healthcare providers will gain understanding into how health outcomes in male and female Service Members may be affected in unique

ways. To support gender-based research efforts in the Military, researchers at NHRC, funded by EACE, critically examined what types of combat-related injuries military women sustained in recent conflicts. The researchers also investigated the likelihood of leaving active military duty after a deployment-related injury, as well as an examination of acute care medical resource usage in the severely injured female population. Service Women who sustained combat-related injuries in OIF or OEF between January 2003 and May 2014 were identified from NHRC's EMED. Injuries were then characterized using AIS and International Classification of Diseases, 9th Revision codes (ICD-9). For study purposes, 844 combat-related injury episodes in women were used from EMED. Fifty-one percent (n = 433) were OIF injuries and 49 percent (n = 411) were OEF injuries. Blast events were responsible for 90 percent of injuries.<sup>127,128</sup> The average ISS was three, with no statistical difference in means between OIF and OEF. Of significance were increased head injuries in OEF compared with OIF (80 percent versus 48 percent;  $p < 0.001$ ). Although the majority of combat-related injuries suffered by women were mild, some women suffered life-threatening injuries, and nearly 65 percent of the injury episodes resulted in more than one injury. In-patient hospital days averaged 31.6 days post-injury in women with severe injuries (ISS > 9). At the time of this study, more than 65 percent of the injured women remained on active military status, either active duty, Reserve, or National Guard. Future studies will investigate QOL outcomes and gender differences in combat-related injuries.

### **Increased Prevalence of Metabolic Syndrome among Combat Veterans with Lower Limb Amputation**

Studies of World War II Veterans found relatively high rates of cardiovascular disease (CVD), including long-term mortality following combat-related amputations.



Photo credit: Sean Kimmons/US Air Force

However, little research has described risk factors for CVD including metabolic syndrome among Service Members who sustained lower limb amputations in the Iraq and Afghanistan conflicts. Approximately 90 percent of these combat amputations were caused by blast injuries. This study, funded by EACE, described CVD risk factors, including metabolic syndrome for patients with lower limb amputations and those with serious lower extremity injuries without amputation.<sup>129</sup> Researchers at NHRC and VA at the San Diego VA, with funding from the Navy BUMED WII Program, identified study patients and injury-specific data in NHRC's EMED. Patients were injured in Iraq and Afghanistan between 2001 and 2008 and had serious lower limb injury without amputation (n = 162), unilateral (n = 380), or bilateral (n = 134) lower limb amputations. VA national data sources provided CVD measures over an average of five years post-injury. These measures included blood pressure, body mass index (BMI), high- and low-density lipoprotein cholesterol (HDL, LDL), and metabolic syndrome. Researchers found significantly increased likelihood of CVD risk factors, particularly following bilateral amputation compared with no amputation. These elevated risk factors included HDL

and metabolic syndrome. Importantly, the association between amputation and increased metabolic syndrome was significant only for patients with high BMI (greater than 28 kilograms per meter<sup>2</sup>). For patients with high BMI, the prevalence of metabolic syndrome was 11.5 percent among Veterans without amputation versus 25.9 percent and 32.7 percent for Veterans with unilateral or bilateral amputation, respectively. The present study indicates that lower limb amputation, and particularly bilateral lower limb amputation, is associated with increased CVD risk. The study identifies an important modifiable variable, namely bodyweight or BMI, which is associated with increased likelihood of metabolic syndrome for patients with lower limb amputations. The results support the need for primary care and lifestyle interventions to manage weight and lipid levels, particularly following combat-related amputations.

### **Five-Year Health Outcomes Following Upper Limb Combat Amputations**

Service Members who sustained combat amputations to the upper limbs in the Iraq and Afghanistan conflicts present new challenges for military and VA providers. Approximately 90 percent of these amputations were caused



by blast injuries. Little research has tracked their health outcomes beyond the short-term due to the difficulty of integrating military and VA health data. This study, funded by EACE, described the physical and psychological outcomes for US Service Members during the first five years following upper limb amputations sustained in Iraq and Afghanistan, 2001–2008. Researchers compared clinical diagnoses for patients with upper limb amputations to individuals with serious upper limb injuries without amputation. Researchers at NHRC, NMCS, and San Diego VA—with funding from the Navy BUMED WII Program—identified study patients and injury-specific data in NHRC’s EMED. The study team conducted a retrospective review of military and VA health databases for patients who sustained unilateral upper limb amputation (n = 141) or serious upper limb injury without amputation (n = 85) in the Iraq and Afghanistan conflicts, 2001–2008. Military and VA health diagnoses were followed for five years post-injury for all patients. Patients with above elbow (AE) amputations had significantly higher ISS than patients with below elbow amputations (BE) or no amputation. The AE group had significantly higher prevalence of anemia, PE, osteomyelitis, and eye disorders compared with BE amputation patients and/or upper limb injury without amputation. By contrast, neuroma was significantly more likely following BE than AE amputation or no amputation. The prevalence of HO was 11–21 percent and highest following AE amputation. All groups had similar relatively high incidence of lumbago and/or limb pain (40–60 percent), hypertension (15–20 percent), and obesity diagnoses (12–19 percent). The five-year incidence of osteoarthritis ranged between 8 percent and 15 percent with no significant differences between groups. Nearly 90 percent of all groups had at least one psychological disorder. The prevalence of PTSD increased significantly after the

first year for the amputation groups, while diagnoses of mood, anxiety, and adjustment disorders declined over the first five years post-injury for all groups. This is one of the first studies to integrate military and VA health records for five years after combat amputations to the upper limbs. It is also one of the first to describe how physical and mental health outcomes following upper limb amputation may be unique by comparison to patients with serious upper extremity injury without amputation. These results can help refine existing treatment strategies to prevent early wound complications and other physical and psychological health complications. The results can also guide development of post-injury treatment pathways for patients with upper limb amputation versus other serious upper extremity trauma.

### **Five-Year Health Care Utilization Trends Following Combat Amputation**

Over 90 percent of patients who sustained major limb amputations in the Iraq and Afghanistan conflicts have received care from both DoD and the VA medical facilities in the years after injury. Little previous research has described the types of clinics and care received at these facilities, the post-injury timing for the various types of care, and the levels of patient flow and/or care between DoD and VA facilities. This had been partly due to the difficulty of accessing and integrating DoD and VA health data. As part of the ongoing work of defining and understanding the extremity trauma and amputation populations, the EACE funded this study. The present study population was 581 patients who sustained combat-related, unilateral limb amputations from 2003–2008, representing approximately 95 percent of the unilateral amputation population for that period.<sup>130</sup> Patients were divided into upper extremity (n = 141) and lower extremity groups (n = 440), and their clinical experience was tracked for five years

post-injury using both DoD and VA national databases, with the last patients completing five year follow ups in 2013. DoD clinic codes are recorded as Medical Expense Performance Reporting System codes, while the VA uses Decision Support System identifiers, commonly referred to as Stop Codes. For some clinic types, there is not a one-to-one correspondence between the DoD and the VA clinic codes. Overall results were tracked year-to-year over the five-year period for those who stayed in DoD clinics, those who migrated to VA clinics, and those who used both DoD and VA clinics. For most patients in the unilateral amputation group, there was not a distinct transition from DoD clinics exclusively to VA clinics exclusively. Rather the majority used both DoD and VA clinics in the first two years post-injury. The overall result was a steady decline in the percentage of patients treated at both DoD and VA facilities in the same year, and a sharp rise in the percent of patients treated exclusively at VA facilities. Gradual but significant declines in the use of DoD clinics from year one post-injury to year three post-injury were seen in the physical and occupational therapy clinics as well as the orthopedic and psychiatric clinics. By the fifth year post-injury, over 75 percent of the upper and lower amputation groups had migrated exclusively to VA clinics, with the social work, mental health, and physical therapy clinics having the largest number of patients. While most patients with major limb amputations transitioned to VA clinics within five years post-injury, the transition from DoD clinics was gradual, with the majority of patients using both DoD and VA clinics for several years. Possible future research should include more in-depth analysis of specific clinic types and examination of usage patterns by demographic or health condition subgroups.

This research provides an initial evidence base to help DoD and VA healthcare systems and providers improve planning



Photo credit: Samantha L. Quigley/US DoD

and coordination for the multiple years of rehabilitation care required following combat-related amputations. To our knowledge, the present study provides some of the first results to identify the different types and post-injury timing for outpatient clinical care used by patients as well as whether the care is provided by DoD, VA or both healthcare systems. Ultimately this research can optimize long-term clinical treatment pathways for patients with combat-related amputations.

### **Assessment of Outcome Measures to Evaluate the Performance of Advanced Upper Limb Devices**

As upper extremity prosthetic devices continue to advance, it is unclear if traditional outcome measures accurately assess their impact on function and QOL. Researchers from CRSR at USUHS evaluated currently available assessments of QOL (Box and Blocks Test, Southampton Hand Assessment Procedure, and Assessment of Capacity for Myoelectric Control) in a Vietnam Veteran

using an advanced DEKATM prosthetic. Data showed that currently used upper extremity prosthetic assessment tools are inaccurate when assessing the impact that advanced prosthetic systems have on the perceived QOL because the assessments lack qualitative elements and QOL metrics that are important to populations using modern prosthesis. The findings of this research caution against using these assessment tools and suggest that there is a need to develop better tools for assessing QOL.

### **Biomechanical Variability with Changes in Cognitive Demand during Ambulation for Service Members with Lower Limb Amputations**

Learning to walk with a prosthetic device following lower limb loss poses distinct challenges on cognitive and motor functions, and the long-term implications on performance in each task has not been identified. Assessments of biomechanics and cognitive function while performing a dual task by researchers funded by CRSR at USUHS have demonstrated that ambulation imposes an additional cognitive workload for both individuals with and without lower limb loss, and there may be additional considerations for individuals with limb loss because of a potential added cognitive workload required to ambulate with a prosthesis. This additional workload may require the body to reduce attentional resources from walking mechanics when there is a need to focus on a secondary task, potentially increasing the risk of falls in these individuals. Additional treatment techniques, to include novel rehabilitation training and/or more intuitive prosthetic componentry, may need to be developed to reduce this additional workload in the lower limb loss population, reducing the cognitive burden and risk of falls. Gaining a better understanding of the mental/subconscious workload of walking with a prosthesis can help identify

treatment techniques to diminish this burden, potentially reducing mental fatigue and/or the risk of falls from distracted walking.

### **Lower-limb Amputation and Effect of PTSD on VA (Outpatient Cost Trends)**

Researchers at the NHRC, with funding from EACE, studied costs of VA outpatient care among patients who sustained serious leg injuries in combat in Iraq and Afghanistan between 2001 and 2008 by comparing costs for Veterans who had either a serious leg injury without amputation (n = 170), one leg amputation (n = 460), or amputation of both legs (n = 153). Patients with amputation(s) had more than double the VA outpatient costs compared to patients without amputation. Average VA outpatient costs per year in 2012 were \$7,200 for serious leg injury without amputation, \$14,700 for unilateral leg amputation, and \$18,700 for bilateral leg amputations. Annual VA costs declined significantly after the first year in the VA for Veterans who had a serious leg injury without amputation. By contrast, annual costs doubled over 3–5 years in the VA for patients with unilateral or bilateral amputation. Among patients with amputation, durable medical equipment (DME), including prosthetics) accounted for more than 50 percent of outpatient costs. In addition, PTSD is common among these patients and is known to complicate rehabilitation following combat injury. PTSD also predicted increased VA outpatient costs. The higher VA costs for the care of patients with PTSD show the importance of early treatment of PTSD to reduce long-term VA costs for patients with serious leg injuries and especially those with amputation. Overall, amputation and PTSD were associated with significantly increased VA outpatient costs based on multivariable regression models. Amputation was associated with a 3.12-fold increase in mean DME cost per year. PTSD was associated

with significantly increased DME cost by amputation status and significantly increased psychiatric and pharmacy costs. Increasing ISS was also associated with significantly increased costs.

This study is one of the first on outpatient costs at the VA over an average of five years for Veterans who had serious leg injuries, including amputation in the Iraq and Afghanistan conflicts.<sup>131</sup> The results indicate relatively high and sustained outpatient costs over years at the VA, for patients following lower limb amputation that is largely driven by the cost of prosthetics. PTSD substantially increased costs for multiple domains of healthcare including rehabilitation, pharmacy, and psychiatry. This finding highlights the importance of accurate diagnosis, treatment, and support for PTSD to reduce long-term healthcare costs. Understanding healthcare costs is a key to deliver timely and appropriate care to optimize outcomes for the nearly 2000 Service Members who sustained major limb amputations during the Iraq and Afghanistan conflicts. Given that extremity injuries accounted for approximately 50 percent of all combat injuries in these conflicts, it is important to understand healthcare costs following combat-related extremity injuries in order to support this large population of Veterans in the long term.

### **Long-term QOL Outcomes in Injured Tri-Service Service Members: The Wounded Warrior Recovery Project**

The long-term effects of blast-related injuries and diagnoses are not well understood. To better understand the consequences of these combat injuries on Service Members' long-term health and readiness, the NHRC in San Diego, California, is longitudinally assessing clinical, rehabilitative, and QOL outcomes in injured Service Members. This project, named the Wounded Warrior Recovery Project (WWRP), is being conducted with funding support from the Navy BUMED under the WII Program and the DoD/VA EACE. Each of the more than 55,000 Service Members injured in Iraq and Afghanistan beginning in October 2001 is currently being contacted and invited to participate in WWRP. WWRP is a 15-year, longitudinal, prospective, population-based survey study of injured Service Members, with surveys being administered every six months to gauge physical health, mental health, and QOL outcomes. To date, 4,235 injured Service Members have provided informed consent and enrolled in the study and over 13,000 surveys have been collected. Approximately 79 percent of respondents were injured in a blast event (Table 7-2). In all respondents, injuries to the head and spine are associated with worsened psychosocial

**TABLE 7-2:** Characteristics of Wounded Warrior Recovery Project (WWRP) Respondents

<b>Demographic Averages</b>	<b>Branch of Service (%)</b>		<b>Mechanism of Injury (%)</b>	
98% Male	Army	67%	IED	64%
33 years of age (SD=7.2)	Marine Corps	29%	Non-IED blast	15%
4.8 years since injury (SD=2.9)	Navy	3%	Gunshot wound	11%
	Air Force	1%	Other mechanism	10%

Used with permission of the authors Susan I. Woodruff, PhD, Daniel Sack, Susan Eskridge, PhD, and Michael Galarneau, MS NREMT



outcomes. Future follow-up surveys will integrate more specific measures of interest, including pain and social support, and prosthetic use/satisfaction in the amputee population. These discrete measures may provide insight into the nexus between QOL and specific target areas of concern, as well as focus on severe blast injuries. This study is being conducted predominantly online, with supplemental telephone and paper surveys for those Service Members who cannot respond online. The project's public facing website can be viewed here: [www.wvrecoveryproject.org](http://www.wvrecoveryproject.org).

WWRP is the first and only initiative to longitudinally study injured Service Members and examine their long-term physical health, mental health, and QOL outcomes after combat injury. By assessing long-term QOL outcomes, NHRC, EACE, DoD, and VA can evaluate those clinical treatments, rehabilitative programs, and prosthetics/orthotics that are actually moving the QOL meter for injured Service Members and those that are not. This not only results in immediate and real improvement in the quality of care delivered, but also in immense cost savings now and throughout the lifetime of care that many of these Service Members will require. WWRP continues to produce manuscripts, presentations, technical reports, and recommendations.

### **Assessing the Health Effects of Blast Injuries and Embedded Metal Fragments**

Many of the common wounds of the current and recent conflicts in both Iraq and Afghanistan have been the consequence of Service Members coming into contact with IEDs resulting in traumatic injuries and wounds contaminated with toxic metals. This contamination with toxic metal potentially poses additional health threats to the Service Member arising from acute and long-term exposure to embedded fragments. Due to potential complications from surgeries to

remove these fragments and the historical belief that metal was not thought to be harmful, the conventional wisdom was that it was safe to allow the metal fragments to remain in place. However, in recent years as researchers have learned more about the potential health threats caused by leaving unidentified metal fragments within the body, this policy has come under question. In addition, since the composition of the fragment is often unidentified and the toxicological properties and carcinogenic potential of these fragments is unknown, clinicians are left with little information upon which to base treatment decisions.

With funding from the Peer Reviewed Medical Research Program (PRMRP) managed by CDMRP, this project proposes to leverage long-standing collaborations between the Armed Forces Radiobiology Research Institute and the VA Depleted Uranium and Toxic Embedded Fragment (TEF) Surveillance Centers in order to bring together a complementary set of both animal and human studies in order to address this challenge. The four studies included in this project are: (1) "Health Effects of Embedded Fragments of Military-Relevant Metals" that will examine the absorption and effects of embedded fragments in tissue of animals implanted with metals of toxic concern; (2) "Biomarkers for the Early Detection of Adverse Health Effects Resulting from Embedded Metal-Fragment Wounds" that will identify early biomarkers of tissue injury that may signal the need for fragment removal; (3) "Biomarker Assessment of Kidney Injury from Metal Exposure in VA-TEF Registry Veterans" that will assess biomarkers of early kidney damage in Veterans registered in the VA-TEF registry and injured with a fragment; and (4) "Respiratory Health in a Cohort of VA-TEF Registry Veterans Exposed to Blasts and Metals" that will examine lung function and insult from both metal inhalation and blast effects from the traumatic injury in this same VA-TEF Registry



Photo credit: Sara E. Martin/US Army

cohort. Together, these projects will address the specific knowledge gaps currently challenging the care of embedded fragments and blast injury patients. It will specifically focus upon enlarging our knowledge base regarding military-relevant metals and their behavior in the body. Ultimately, the results of this project will provide the evidence base to support medical decision-making in the care of the estimated 40,000 Veterans injured in recent conflicts.

## Neurobehavioral and Psychological Health Outcomes

### **Defining the Genetic Changes after Blast Injury to the Retina**

Researchers and clinicians in the Department of Ophthalmology at Emory University are characterizing the effects of 48 pounds per square inch blast injury to the eye and retina. They are using a mouse model and a complex genetic analysis to define the molecular changes occurring in the retina following blast injury. The microarray datasets include one

dataset from naïve uninjured mice (58 strains of mice and 222 microarrays looking at over 50,000 genomic elements) and a second dataset from mice five days after a blast injury to the eye (54 strains of mice and 213 microarrays). These large datasets provide the power to see changes caused by the blast injury for the very first time.<sup>132, 133</sup> They have identified highly significant (false discovery rate < 0.001) changes in 13,971 genomic elements. Although the analysis is not yet completed, there are several themes emerging from the data. Following blast injury, there is a modest but real decrease in genes associated with metabolism. There are also changes associated with the normal functioning of cells in the retina. Many of the genes increasing in expression following blast injury are associated with the innate immune system and the chronic infiltration of T-cells. To investigate the possibility that lymphocytes were invading the retina, the study team examined a blast eye seven, 14 and 21 days following the initial injury and found

a significant number of invading T-cells. Together the data point to an insidious cascade of events that may be slowly altering the normal functioning of the retina. In the mouse model, there is a progressive loss of visual function that proceeds for at least two months. The molecular events seen at five days after blast injury may be the beginning of events that lead to this loss of vision. Researchers are now examining the changes in the retina to identify potential drug targets that could alter or stop the observed genetic changes with the hope that stopping this detrimental process should halt or reverse the loss of vision. These studies are funded by the PH/TBIRP managed by CDMRP.

#### **Hearing Fitness for Duty and RTD Assessment and Validation**

This study is performed by researchers at Creare Inc. and is managed by CDMRP. The objective of this study is to develop and validate a military-specific hearing test that can be used as a part of a hearing fitness-for-duty (HFFD) and RTD assessment battery. The test will provide information on a Service Members' ability to recognize relevant sounds, the effect of hearing loss on this ability, and the effect of wearing hearing protection devices. The proposed effort will put HFFD and RTD tests in the hands of military audiologists within one to three years. These tests will be validated and vetted by military audiologists, Service Members, researchers, and fitness-for-duty experts. During FY16, the investigators completed manufacturing and initial assembly of 40 of the HFFD systems that will be used to carry out validation studies on normal hearing, non-military adults in collaboration with partners at the University of Connecticut. The technology produced under this award will provide military audiologists validated tools to evaluate functional hearing of Service Members.

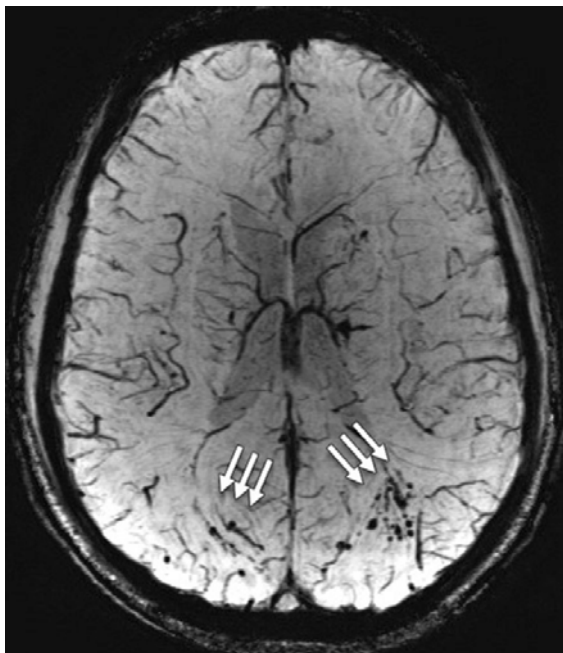
#### **Findings from Structural MRI in Military TBI**

Researchers at NICoE investigated the effects of chronic mTBI in Service Members using an integrated MRI protocol. The predominant form of TBI in deployed personnel occurs as a result of blast injury. Blast injury may be associated with higher rates of sensory impairment, neuroimaging findings, and emotional impairment. However, this has not been a consistent finding in military populations. This study described the neuro-radiological findings by using radiological common data elements in an integrated MRI protocol. Participants included a control group without TBI (n = 42), which consisted of active duty Service Members or dependents. The second group consisted of individuals who received a TBI (n = 834). The primary measure was anatomic MRI, which focused on structural aspects of TBI. Additional parameters, identified as neuroimaging common data elements, were also collected for comparison. In this patient population, the most common finding was white matter T2-weighted hyper-intense areas, occurring in 51.8 percent of the blast injured patients (Figure 7-26).<sup>134</sup> Cerebral micro-hemorrhage did occur in a small percentage of the patients (Figure 7-27).

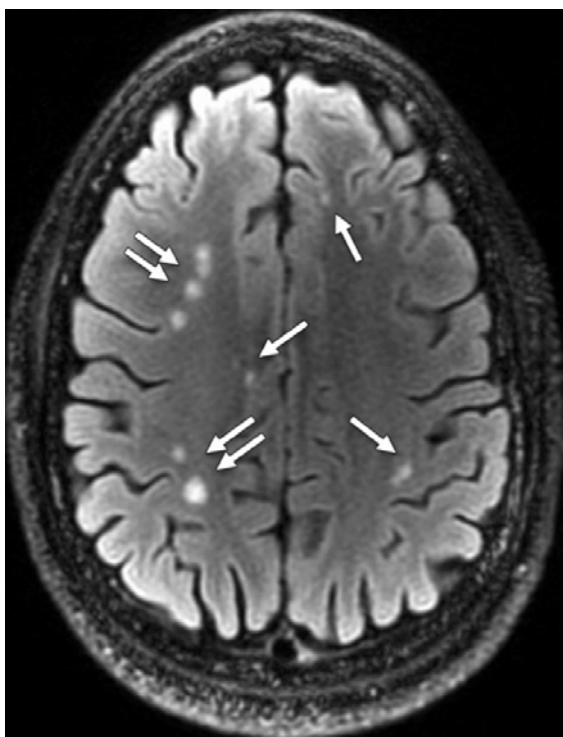
#### **Compromised Neurocircuitry in Chronic Blast-related mTBI**

Researchers at DVBIC and NICoE used DTI techniques to investigate architectural changes in the brain following blast injury. A number of projection fibers are vulnerable to blast injury, which could significantly impact communication and information exchange between regions of the brain. However, the published results thus far in this field are not conclusive. This study attempted to assess architectural changes in blast-injured brains, evaluate the effect of time on those changes, and evaluate the relationship with numbers of injuries. Participants included a

**FIGURE 7-26:** Susceptibility-weighted image shows extensive microhemorrhage (arrows) consistent with diffuse axonal injury in a 25-year-old man with blast-related mTBI. (used with permission of the authors)



**FIGURE 7-27:** Axial T2 FLAIR image shows multiple white matter T2-weighted hyperintense areas (arrows) in a 28-year-old man with blast-related mTBI. This patient had a total of 76 lesions on all sections. (used with permission of the authors)



total of 242 active duty male Service Members, which included a healthy control group (n = 40) and a group (n = 202) that reported persistent post-concussion symptoms for more than six months after a blast-induced mTBI. The primary measure was DTI. However, neuropsychological assessments were also performed, including the Brief Visuospatial Memory Test-Revised, Conners Continuous Performance Test, California Verbal Learning Test, Dells-Kaplan Executive Function System, Rey Osterrieth Complex Figure, and Wechsler Adult Intelligence Scale. The results of this study show that the number of blast events and the time since injury are associated with white matter microstructural injury.<sup>135</sup> However, it should be noted that post-concussive and PTSD symptoms are also associated with compromised neurocircuitry and disruption of the communication and information exchange between regions of the brain.

### **Blast-induced mTBI and Possible Association with PTSD**

Due to the high prevalence of TBI and PTSD in military populations, work at the NMRC has focused on understanding the role of blast-induced mTBI in the development of PTSD. Specifically, changes in anxiety behavior, stress response, and a specific fear-related brain protein, stathmin, have been identified in a rat model of blast-induced mTBI. Stathmin, a protein that has been correlated with states of both innate and learned fear, was elevated in the amygdala of blast-exposed rats.<sup>136</sup> Such findings suggest that blast-related mTBI may contribute to the development of PTSD. Current work refines the behavioral changes seen following blast-related mTBI and utilizes a stathmin knock-out mouse model to further explore the role of stathmin in the development of PTSD. Additional work examines changes in the hypothalamic/pituitary/adrenal axis following mTBI and may lead to a better understanding of the anatomic basis for the PTSD-related traits observed following blast exposure. The findings



from this research will aid in evaluating comorbidity of TBI and PTSD.

### Tympanoplasty Following Blast Injury

Blast-related ear injuries are a concern during deployment because they can compromise situational awareness and impact operational readiness. In this study, the authors report the success rates for tympanic membrane repair following blast-induced perforation. Data was obtained from the NHRC's EMED on the success rates for initial and revision surgical repair of blast-induced eardrum perforations. Furthermore, this study reports the degree of hearing improvement pre- and post-surgery, the proportion that required ossicular reconstruction, the rate of success based on the size of the perforation (percent total surface area), anatomic location of perforation, and elapsed time between injury and surgery date. The proportion of complications, such as cholesteatoma and lateralized tympanic membrane, are also reported. Success rates for surgical repair and functional hearing outcomes from 350 cases are reported, and the intraoperative surgical details are described. A retrospective chart review was conducted of military personnel in the EMED from October 2005 to July 2014. Overall, 255 patients with blast-related tympanic membrane perforations were identified using ICD-9 Clinical Modification diagnostic codes.

Study variables included initial and revision success rates for tympanoplasty, frequency of ossiculoplasty and cholesteatoma (minimum one year follow-up), pre- and postoperative audiometric measures (pure tone average [500 Hertz to three kilohertz], air bone gap, speech recognition threshold), perforation size (percent surface area), annulus involvement, and time elapsed between injury and surgery. There were a total of 350 surgeries (300 initial and 50 revisions) amongst 255 subjects. One hundred eighty-three patients had only one surgery, while 72 patients required multiple surgeries. For initial surgery, there was an 81.3 percent success rate (244/300) and for revision cases the success rate was 82 percent (41/50). The mean hearing improvement based on Speech Reception Threshold was 14.35 decibels ( $\pm 12.04$ ). Subsequent cholesteatomas were developed in 12.3 percent (37/300) of patients and 10.7 percent (32/300) required ossicular chain reconstruction. There was no significant effect of the length of time between initial injury and surgery or the perforation size with regard to the rate of successful perforation repair (Table 7-3). Ear injuries and auditory hearing impairment are frequent consequences of blast exposure during combat deployment. Success rates for blast-induced perforations are lower than that of other common injury mechanisms. Because of cholesteatoma development rates, close clinical

**TABLE 7-3:** Optimal Observation Period

Healed		Not Healed	
<3 months	56	<3 months	10
3-6 months	85	3-6 months	19
6-9 months	47	6-9 months	8
>9 months	58	>9 months	18
Mean # days:	191.4 ( $\pm 137.0$ )	Mean # days:	228.8 ( $\pm 249.8$ )

(t-test was not significant at the 0.05 alpha level,  $t(298) = 1.803$ ,  $p = 0.07$ )

surveillance is required. Results can help guide clinicians in the timing of repair and the expected postoperative outcomes.

### **Prevalence and Objective Verification of Central Auditory Processing Disorders in Blast-Exposed Warfighters**

After the start of OEF and OIF, DoD and VA audiologists began seeing increasing numbers of blast-exposed Service Members with relatively normal audiograms, but who subjectively report difficulties understanding speech in noisy environments. However, estimates of the scope of this problem are unknown and there are reasons to believe the traditional hearing loss metrics based primarily on a pure-tone audiogram and standard speech tests may underestimate the degree of damage to the hearing system. Accurate comprehension of speech relies not only on an intact sensory system, but also on cognitive abilities such as attention and working memory. Therefore, researchers

at WRNMMC, NMCSD, and Wilford Hall Ambulatory Surgical Center have established a multi-site infrastructure for large-scale data collection. This research addressed three major aims: 1) determine the prevalence of functional hearing difficulties among blast-exposed Service Members with normal to near-normal hearing as designated by the Army profiling system (H1 profile - AR40-50I); 2) identify sensory and cognitive factors that may contribute to difficulty with speech communication; and 3) develop a clinically appropriate battery of tests to diagnose these deficits. To accomplish these three aims, the research team developed a tablet-based test environment that could be deployed and controlled remotely and that included both hearing and survey tests to determine functional hearing ability in a large population. In addition, a PC-based test battery for assessing functional hearing and communication deficits was developed, including test selection and hardware and

**FIGURE 7-28:** PC-based Test Battery for Assessing Functional Hearing and Communication Deficits



software development for auditory and visual peripheral, central, and cognitive communication processing tests (Figure 7-28).

Hearing problems are among the top disabilities reported by returning Service Members. Concurrent injuries to the auditory system as a result of acute blast trauma and resultant TBI account for 25 percent of all war injuries.<sup>137</sup> DoD and VA have observed concomitant damage to the central auditory structures of the brain. The magnitude of the problem of auditory processing in returning Service Members is unknown. The results from this project are likely to influence regulations for auditory fitness for duty and accession and retention standards for individuals with and without normal audiograms. Current guidelines for retention and accession standards for individuals with normal audiograms are without limit, assuming that a finding of normal hearing thresholds indicates normal hearing. It is now known, as this study shows, that this assumption is false. The audiogram is a useful tool for measuring hearing but it is limited and does not measure understanding or processing of what has been heard. In military situations, the failure to adequately understand speech commands or to interpret environmental sounds correctly can be life-threatening to the Service Member and to those around him/her. Preliminary results suggest that even the mildest hearing loss coupled with a history of blast exposure can render an individual's ability to hear and understand auditory input roughly five times worse than a non-blast-exposed Service Member. These results will likely influence policy standards regarding auditory fitness for duty.

#### **Characterization of Interface Astroglial Scarring in Human Brain after Blast Exposure: A Postmortem Case Series**

No evidence-based guidelines are available for the definitive diagnosis or directed

treatment of most blast-associated TBI, partly because the underlying pathology is unknown. Moreover, few neuropathological studies have addressed whether blast exposure produces unique lesions in the human brain, and if those lesions are comparable with impact-induced TBI. Researchers at USUHS hypothesize that blast exposure produces unique patterns of damage, differing from that associated with impact-induced, non-blast TBIs. In this postmortem case series, the study team investigated several features of TBIs, using clinical histopathology techniques and markers, using brain specimens from male Service Members with chronic blast exposures and from those who had died shortly after severe blast exposures.<sup>138</sup> They compared these results with those from brain specimens from male civilian (e.g., non-military) cases with no history of blast exposure, including cases with and without chronic impact TBIs and cases with chronic exposure to opiates, and analyzed the limited associated clinical histories of all cases. Brain specimens from five cases with chronic blast exposure, three cases with acute blast exposure, five cases with chronic impact TBI, five cases with exposure to opiates, and three control cases with no known neurological disorders were analyzed. All five cases with chronic blast exposure showed prominent astroglial scarring that involved the subpial glial plate, penetrating cortical blood vessels, grey-white matter junctions, and structures lining the ventricles; all cases of acute blast exposure showed early astroglial scarring in the same brain regions. All cases of chronic blast exposure had an antemortem diagnosis of PTSD. The civilian cases, with or without a history of impact TBI or a history of opiate use, did not have any astroglial scarring in the brain regions analyzed.

An important component of TBI occurring among Service Members on the battlefield relates to exposure to blasts produced by

## CLINICAL PRESENTATION OF CASE 1

Case 1 was a 45 year old male veteran who died from a self-inflicted gunshot wound. During his 25 year military career he received numerous commendations, and colleagues considered him highly competent, reliable, and emotionally stable.

According to members of his team, they routinely experienced blast exposures during training exercises and combat missions with bombs landing or improvised explosive devices (e.g., those made and deployed not according to standard military procedure) detonating in close proximity. With blast exposure, team members described a jolting sensation and noted that these incidents commonly resulted in post-concussive like symptoms. After retirement, the patient admitted to multiple mTBIs during his military service, but had chosen not to report his symptoms at the time for fear of being deemed unfit for duty. He complained of headache and memory problems and described trouble maintaining mental focus, which he attributed to severe sleep disturbance. He often lost coherence of thought and jumbled his speech. His wife reported that he experienced cognitive and behavioural changes. For example, she described his abnormally slow hand movements over the car steering wheel, ignition and gear shift, as if confused about their functions. Formerly superior in spatial concepts, he struggled to pack the car for holiday travel. He failed to remember family plans. On several occasions, he became uncharacteristically angry with her. Clinicians described poor eye contact, flat affect, and low voice tone, and treated him for PTSD, depression, and anxiety. One month before he died, conventional MRI (1.5 T) showed no brain abnormalities. No formal report of TBI could be found in his medical records. His wife recounted that he had wrestled and boxed during his school years and experienced three motor vehicle accidents throughout his life. There was no indication of substance abuse by medical history or post-mortem toxicology screening.

**PANEL:** Clinical Presentation of Case 1 from Publication <sup>138</sup>

high explosives, primarily through the use of IEDs and suicide bombs by the enemy. Identification of this unique and characteristic pattern of brain damage related to blast exposure, as discovered and described in this publication, may begin to explain why large numbers of Service Members exposed to such weapons return from deployment with persistent and troublesome neurologic and behavioral symptoms, such as chronic headaches, sleep disorders, problems with concentration and memory loss, depression, irritability, and abrupt mood swings ranging from agitation to despair, sometimes leading to suicide. It is hoped that these findings will lead to better and more targeted approaches to diagnosis, treatment, and prevention of these serious sequelae following participation in modern warfare.

## CENC

CENC is a dedicated joint DoD and VA effort addressing the long-term consequences of mTBI in Service Members and Veterans. It is conducted in response to the Presidential Executive Order 13625 and aligned to the NRAP for Improving Access to Mental Health Services for Veterans, Service Members, and Families. The CENC Coordinating Center is located at VCU and executes 10 studies and five integrated research cores across more than 30 participating institutions (<https://cenc.rti.org>). The majority of studies are focused on human subjects recruited from Veteran, active duty Service Member, Reserve, and National Guard populations. CENC studies examine chronic TBI and co-morbidities associated with mTBI; sensory deficits (visual, auditory, vestibular), movement disorders, pain (including headache), cognitive, and neuroendocrine deficits. All studies include data from populations with blast exposure. For instance, in a recent study accepted for publication in *Brain Injury*, case reports were collected on four Veterans at the James A. Quillen VA who





were reporting chronic dizziness and postural instability following blast exposures.<sup>139</sup> Analysis of neuroimaging data collected on these Veterans demonstrated diffuse axonal injuries and micro-hemorrhages or vascular anomalies as measured using DTI and susceptibility weighted imaging respectively. The association between neuroimaging biomarkers and long-term outcomes will be further investigated in a recently initiated CENC-supported study at the WG Hefner VA that will examine microstructural features in post-deployment Veterans with blast exposure histories to better understand the relationship between neuroimaging findings and chronic cognitive and psychological outcomes.

#### **A Pilot Study to Understand the Differentiating Factors for TBI from PTSD Patients**

TBI has become the “signature wound” of OIF/OEF. Due to the increasing use of IEDs by the insurgency and the necessary facial exposure of our combat troops even when wearing protective gear, estimates suggest that as many as 20 to 30 percent of returning Service Members may eventually exhibit symptoms of TBI. PTSD as defined by the American Psychiatric Association is a serious behavioral health disorder, and it has been estimated that 17.1 percent of Service Members returning from Iraq and 11.2 percent of those returning from Afghanistan have experienced major depression, generalized anxiety, and/or PTSD. As a part of the present effort investigators at the Integrative Systems Biology Program (USACEHR) are working with collaborators from Dwight D. Eisenhower Army Medical Center screening for potential biomarkers associated with neuronal injury. In this pilot study, blood samples were collected and shared with USACEHR for multi-omics analysis for identification of candidate genes/proteins. The candidate gene/protein approach is viewed as only a first step toward identifying molecular mechanisms likely to be involved in the physiologic consequences of TBI/PTSD. Gene

expression, DNA methylation, and targeted proteomics analysis have been completed in these samples (Figure 7-29), and functional pathway predictions show possible overlaps between networks enriched by differentially expressed genes and methylated genes (Figure 7-30). The advancement of the current findings from the USACEHR group needs to be validated using a larger sample size, and it will be important to include a gender/age/ethnicity matched control population. The results of this research will be leveraged in multiple ways to improve the health and treatment of returning Service Members diagnosed with TBI and with PTSD.

#### **Integrated Eye Tracking and Neural Monitoring for Enhanced Assessment of mTBI**

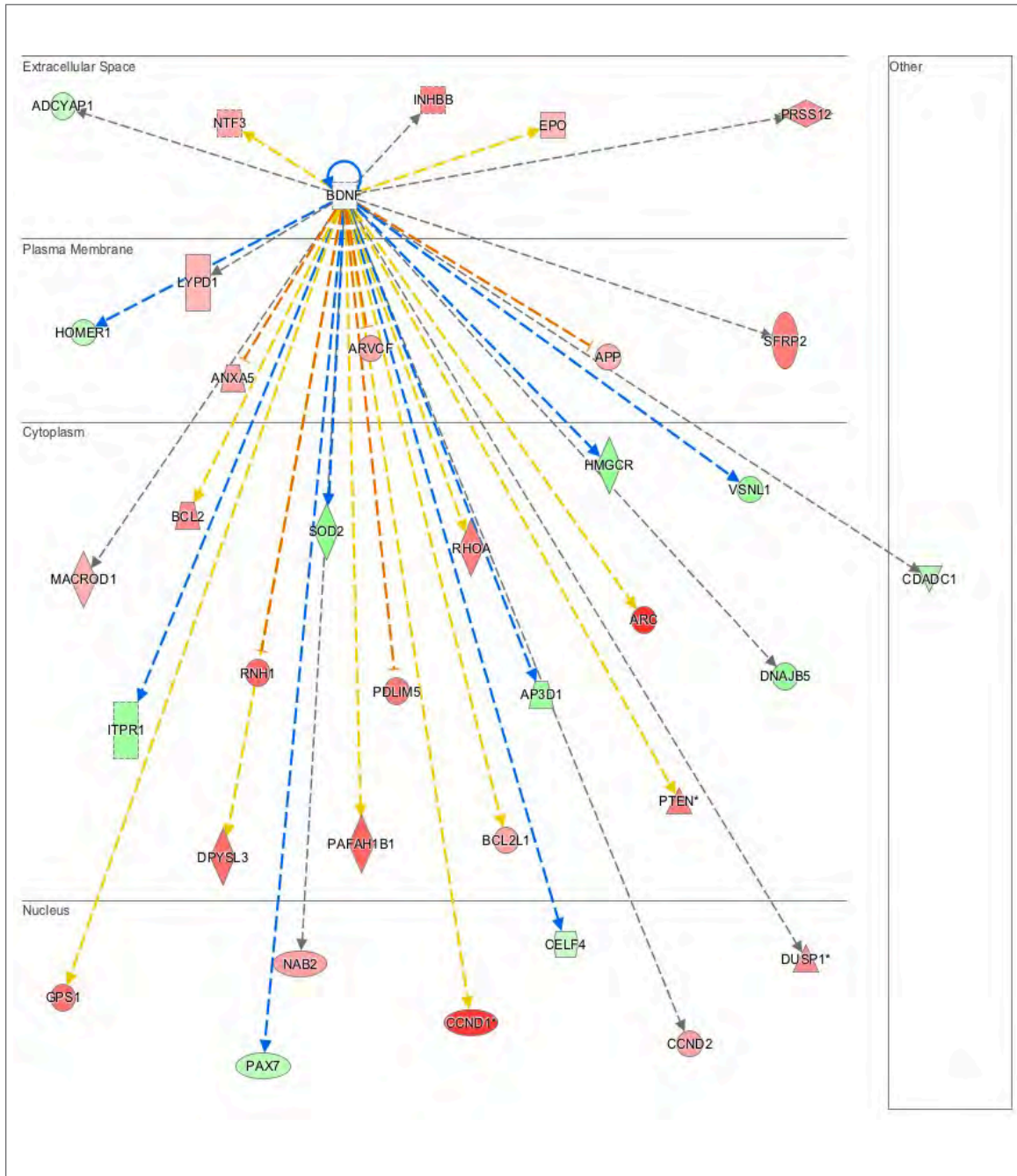
Approximately one in six deployed US Service Members has sustained a mTBI. Identifying and characterizing these injuries is critical to achieving positive operational and treatment outcomes. Neurocognitive measures must be practical for use in a broad range of contexts, from operational settings where injuries occur, to TBI clinics where wounded Service Members work on regaining operational proficiency. Unfortunately, research suggests that commonly used measures are often insensitive to injury-related changes in cognitive function. Researchers from USUHS, NICoE, the Neurocognitive Assessment Branch of the US Army, and NMCS D have been working together to develop and validate a single system for evaluation of mTBI, integrating both EEG-based measures of neurocognitive effort, and eye tracker-based measures of saccadic reaction time. Accomplishments for FY16 include complete development and testing of combined EEG with eye tracking and neurocognitive tests and virtual reality simulation in a small pilot study of 30 healthy human subjects. Preliminary analyses indicate that these cognitive efficacy tasks were successful in discriminating between workload conditions. Hence, the

**FIGURE 7-29:** Pathways Differentially Expressed in Blood Samples from TBI/PTSD Compared to TBI

Ingenuity Canonical Pathways	Upregulation	Downregulation
PI3K/AKT Signaling	11	6
mTOR Signaling	8	6
Protein Ubiquitination Pathway	5	7
Neuregulin Signaling	10	6
Telomere Extension by Telomerase	20	13
PEDF Signaling	13	3
AMPK Signaling	4	7
TGF-beta Signaling	11	2
Cyclins and Cell Cycle Regulation	6	8
VEGF Signaling	10	3
Gap Junction Signaling	7	4
EIF2 Signaling	5	5
p53 Signaling	8	4
CDK5 Signaling	6	6
Telomerase Signaling	5	7
Cell Cycle Regulation by BTG Family Proteins	9	9
NRF2-mediated Oxidative Stress Response	6	4
ErbB2-ErbB3 Signaling	11	4
Ceramide Signaling	8	5
Wnt/beta-catenin Signaling	7	4
PTEN Signaling	9	2
Epithelial Adherens Junction Signaling	7	3
Dopamine-DARPP32 Feedback in cAMP Signaling	5	5
RAR Activation	7	2
Nitric Oxide Signaling in the Cardiovascular System	6	5
Apoptosis Signaling	8	3
Synaptic Long Term Depression	5	5
ILK Signaling	6	3
Axonal Guidance Signaling	4	4
Insulin Receptor Signaling	6	4
Huntington's Disease Signaling	5	3
ERK/MAPK Signaling	5	4
Synaptic Long Term Potentiation	6	4
PPAR Signaling	6	4
NGF Signaling	7	3
Glutamate Receptor Signaling	7	5
Glucocorticoid Receptor Signaling	5	3



**FIGURE 7-30:** Brain Derived Neurotrophic Factor (BDNF) Network Differentially Expressed in Blood Samples from TBI/PTSD Compared to TBI





next phase of the primary study has started using tools developed and tested in the pilot study to access the cognitive functions among these groups: controls (16 enrolled), mTBI (13 enrolled) and moderate-severe TBI (14 enrolled).

Successful validation of a combined EEG and eye tracking system would offer a novel, non-invasive and efficient method of assessing compromised cognitive function stemming from mTBI populations. A practical and effective neurodiagnostic assessment tool for assessing mTBI populations with compromised cognitive function would enable better healthcare and improved health outcomes for injured Service Members.

#### **Evaluation of the King-Devick Test to Assess Eye Movements and the Performance of Rapid Number Naming in Concussed and Non-Concussed Service Members**

This study's objective is to determine to what extent the King-Devick Test results discriminate healthy individuals from both their pre-combat baseline and their post-combat assessment; to determine to what extent individuals diagnosed as having an mTBI event differ from their King-Devick Test pre-combat baseline; and to determine to what extent individuals who report a history of concussion during their pre-combat baseline differ from those who have not reported a prior concussive event. Data collection for this study commenced on 25 July 2016, and 11 subjects have been enrolled (n=100). This study was funded by the DMRDP and is being conducted at Fort Benning, Georgia, in collaboration with Auburn University. The outcomes of this study will inform the military leadership of the neuroanatomical and physiologic changes associated with combat training (both sub-concussive and concussive events) and the research community of

the sensitivity and specificity of various brain imaging techniques compared to neurocognitive measures of interest. In the long run, the findings of this research are expected to lead to preventing concussion associated with training.

#### **Defense and Veterans Eye Injury and Vision Registry (DVEIVR)**

As a part of the organization's mission, VCE generates internal reports using information obtained from the DVEIVR. These reports provide data on operational medicine injuries as a result of combat, occupation, recreational, and habitual activities. VCE generates a Quarterly Report titled "Coordination of Care and Benefits Report" that is provided to Veterans Benefits Administration and Ophthalmology and Optometry Consultants in accordance with NDAA 2008/2009. The purpose of this report is to track Veterans visual acuity of 20/200 or less in the injured eye and/or loss of peripheral vision resulting in 20 degrees or less of visual field in the injured eye. An additional report generated based on the DVEIVR data is the "Newly Injured and Enrolled in DVEIVR Report" that is submitted to VCE Executive Leadership weekly and to Tri-Service Consultants monthly, semi-annually and annually. In addition, VCE initiated a project utilizing the DVEIVR called "Clinical Outcomes of Open Globe Injuries". This project seeks to emphasize that open globe injuries that are often the result of blast events that have serious complications, including a loss of an eye or/and complete vision loss. In addition to an oral presentation at the 2016 annual meeting of American Academy of Ophthalmology, a poster titled "Clinical Outcomes of Open Globe Injuries in the Defense and Veterans Eye Injury and Vision Registry"<sup>140</sup> presented at this meeting was recognized in the "BEST"

category of scientific posters. These reports help to share knowledge about the extent of eye injuries, including blast-related injuries, in military and Veteran populations.

## Neurocognitive and Psychological Health Treatment Strategies

### **Evaluation of a Novel Integrative and Intensive Virtual Rehabilitation Program for Service Members Post TBI**

Researchers at Bright Cloud International Corp created BrightBrainer™, a computerized virtual reality system that provides a combination of cognitive as well as motor skill training in an engaging and repetitive manner. In this clinical feasibility pilot study, researchers will recruit Defense Enrollment Eligibility Reporting System eligible patients with a diagnosis of TBI to participate in a trial of the BrightBrainer™ Virtual Reality Rehabilitation system (BBVR). The objective of this project is to assess the feasibility and clinical benefit of utilizing the BBVR to augment the rehabilitation of Service Members with TBI. To be enrolled, potential subjects must have a diagnosis of TBI and report cognitive, emotional, and/or physical symptoms. In FY16, researchers successfully received scientific and administrative IRB approvals, executed a sub-award agreement, and recruited 11 subjects. The study team has been trained on the Bright Cloud system and has engaged the occupational therapy team. The purpose of the study is to evaluate the feasibility and effectiveness of a novel virtual reality therapeutic rehabilitative device (BrightBrainer™) to treat patients with TBI. These Service Members with TBI, with and without upper limb dysfunction, can use uni- and bi-manual virtual reality exercises to improve cognitive and motor function, as well as mood. If this pilot

study is successful, the study team will work with other healthcare providers to disseminate information and help train others on how to use this system.

### **Enhanced Cognitive Rehabilitation to Treat Comorbid TBI and PTSD**

PTSD and TBI are frequently observed co-morbidities in Service Member and Veteran populations. Traditional Cognitive Process Therapy (CPT), which is often used as a treatment for PTSD, can be limited in efficacy within this population because skills used by the patient in CPT may be inhibited due to chronic cognitive deficits from the TBI. With funding from CDMRP, researchers at the VA Medical Center in San Diego are evaluating an adaption of CPT, referred to as SMART-CPT, which more specifically targets the cognitive deficits often observed after TBI. SMART-CPT is a hybrid training program which combines traditional CPT with Cognitive Symptom Management and Rehabilitation Therapy (CogSMART), a manualized treatment approach used to teach Veterans strategies to compensate for cognitive difficulties. The researchers are conducting a randomized trial of the new SMART-CPT therapy in Iraq and Afghanistan Veterans with mild or moderate TBI and PTSD and comparing it to traditional CPT. During FY16, the investigators were focused on recruitment and data collection for this trial; however, they did observe a preliminary finding where participants in the SMART-CPT group tend to stay in treatment longer than those in the CPT control group. This hybrid treatment has the potential to treat Service Members and Veterans with comorbid PTSD and TBI as opposed to treatment of PTSD and TBI independently. This can potentially lead to changes in CPGs and increase efficiencies in clinical care of affected populations.

### **Serotonin Effects of Blast TBI and Neurocognitive Behavior**

Patients who have experienced blast-induced mTBI are also at an increased risk for developing depression and PTSD compared to the general population through unknown mechanisms. Serotonin is a monoaminergic neurotransmitter synthesized by serotonergic neurons, known to protect the brain due to its antioxidant properties.<sup>141</sup> People with low brain serotonin have reported increased incidence of PTSD.<sup>142, 143</sup> In addition to the brain, other sources of endogenous serotonin are platelets and the small intestine. Characterization of serotonin levels in blood, brain, and intestine in relation to the neurocognitive deficits often experienced in response to blast-induced TBI has not been examined before. This DARPA-sponsored research project conducted by researchers at USUHS is designed to determine the concentration of serotonin in serum, CSF, and small intestine following blast-induced TBI and investigate any associated depression like effects following repeat blast exposures in rats. Male Sprague Dawley rats were exposed to repeat blast TBI followed by evaluations of cognitive deficits. Animals were followed for either seven days or 28 days, at which time tissue samples were collected for serotonin analysis. Researchers found that serum serotonin levels of blast-induced TBI animals were significantly lower than those of naïve animals throughout the 28 day follow-up period. In contrast, serotonin levels in the CSF and small intestine of the blast-induced TBI animals were significantly elevated at day seven, but returned to baseline by day 28. In addition, animals with blast-induced TBI demonstrated depression like behaviors exhibited by less vertical activity in the open field activity measurements at day three and six post blast but subsided by day 28. This suggests an adaptive mechanism of increased serotonin response by the brain and intestine during the initial stages of blast-induced

TBI. Therefore, opportunities may exist for serotonin targeted pharmacological interventions that might benefit at least some components of the cognitive and behavioral symptoms that develop after blast-induced TBI.

### **Hyperbaric Oxygen Therapy (HBOT) in the Treatment of Chronic Mild-Moderate Blast-Induced TBI, PCS, and PTSD**

TBI and PCS severely and disproportionately affect Service Members who have served in Iraq and Afghanistan, with approximately 546,000 having TBI, PCS, and PTSD, yet their treatment options are limited. FY10 Congressional Special Interest funding to Louisiana State University (LSU) and managed by CDMRP supports this study to determine if an eight-week course of forty low-pressure hyperbaric oxygen treatments can significantly improve symptoms and cognitive function in military Veterans and civilians with mTBI and PCS. The proposed design is a randomized controlled (non-treatment, non-sham) single-arm crossover single-blind study. The scope of the project is to recruit, enroll, test, treat, re-test, and follow-up on 50 subjects at LSU. In FY16 the project has continued to enroll subjects and look for ways to improve recruitment. To date, 27 subjects have fully completed the study; three subjects completed the hyperbaric treatment and some post-treatment testing; six subjects have completed the hyperbaric treatment and are in the process of completing their post-treatment testing; two subjects are in the eight-week control period; one subject has been consented and will be randomized; five subjects have signed the screening consent and are moving through the screening process. MTBI causes wounds in the brain, and HBOT has been shown to treat wounds and has duplicated human success in chronic TBI in animal models; therefore, HBOT has the potential to help Veterans with chronic mTBI/PCS. Due to the assessor-blinded study design there

are no preliminary results to report at this time; however, this study offers an effective and economical treatment for PCS and TBI, without the dangerous and negative side-effects of medication.

### **Art Therapy for PTSD and TBI: a Senior Active Duty Military Service Member's Therapeutic Journey**

A clinician at NICoE used art therapy as a therapeutic process for providing treatment for an active duty Service Member with chronic PTSD and a blast-related TBI.<sup>144</sup> This therapy was provided in the context of an integrated care model that included medical and additional complementary therapies. The participant was a senior military Service Member who experienced blast TBI with PTSD. The primary component of the patient's therapy was the creation and discussion of a "mask representing warrior identities" (Figure 7-31). Art therapy sessions, in conjunction with a four-week evaluation and treatment program, significantly reduced the frequency and severity of flashbacks. The patient received art therapy sessions, narrative discussions, and neuroimaging evaluation. This research was sponsored by both the DoD and the National Endowment for the Arts.

### **Evaluation of Extended-wear Hearing Aid Technology for Operational Military Use**

This study is performed at WRNMMC through the Henry M. Jackson Foundation. The objective of this study is to evaluate the ability of a commercially available extended-wear hearing aid to both mitigate the effects of prior hearing loss, and also prevent additional auditory injury from blast and impulse noise. Specifically, the investigators will evaluate if these devices are suitable for Service Members with mild-to-moderate hearing loss for use in austere operational environments that would otherwise preclude the use of normal hearing aid technologies. The study has just begun recruitment and

**FIGURE 7-31:** Patient's Mask Depicting "BFIB" or Bloody Face in Bunker. Photo courtesy of Melissa S. Walker as published in *The Arts in Psychotherapy*.



data collection; however, in the last year they were able to fit two participants with the hearing devices and collect initial pilot data. Additionally, they gained information from an individual who wore the devices during two combat deployments and provided support for the use of these devices in military environments.

### **Brain Training to Enhance Frontal Lobe Reasoning in Soldiers with TBI**

TBI is a leading cause of death and disability within the US with a high occurrence of TBI-related disability within both civilian and military populations. The objective of this collaborative study at the University of Dallas, Texas, was to evaluate the effectiveness of a cognitive rehabilitation therapy after mTBI in Service Members. The study was funded by the DMRDP managed by CDMRP. The Strategic Memory and Reasoning Training (SMART) program was tested for its effectiveness to improve strategic attention, higher-order reasoning, and innovative problem solving in order to





help Service Members return to a productive work life after injury. The investigators used objective measures of cognition, functional life outcomes, and advanced brain imaging techniques to measure the effects of SMART. The study completed recruitment, enrollment, and data collection in FY16, and the study team has several manuscripts under review in peer reviewed journals summarizing the results of this work. Overall, the researchers demonstrated that the SMART program led to gains in cognitive functioning, reduced symptoms of depression, as well as changes in CBF and measures of white matter integrity. Initial results suggest that this program has the ability to improve cognitive capacity and enhance brain function in Service Members through the use of a manualized, evidence-based higher-order cognitive training protocol. The potential to reduce deficits in frontal lobe based executive functions has high relevance to improve outcomes for a population who typically suffer from persistent symptoms long after the initial injuries. Thus, the impact of these studies could enhance Service Members' mental productivity, improve cognitive competence, as well as, reduce the long-term economic burden of TBI-related disability.

### **Treatment of Social Competence in Military Veterans, Service Members, and Civilians with TBI**

Impairments in social competence are among the most prevalent sequelae after TBI. Without successful social skills a person is often isolated, in conflict with others, and denied access to social and vocational opportunities. This project was funded under the PH/TBIRP managed by CDMRP and was performed at Craig Hospital in Englewood, Colorado. The objective of the study was to evaluate Group Interactive Structured Treatment (GIST), a holistic

cognitive-behavioral group intervention aimed at improving social competence impairments for individuals with brain injury. This evidence-based, manualized, 13 week intervention addresses the underlying cognitive, communicative, and emotional impairments impeding social competence following TBI through blending a structured curriculum with a group therapy process emphasizing self-awareness, individual goal setting, group interaction and support, family involvement, and real world applications. Specifically, researchers performed a two-armed, multi-center randomized control clinical trial to study the effectiveness of GIST compared to control treatment (which consisted of the content from GIST presented in lecture format) to improve social competence in participants with social skill deficits after TBI. The study was completed in FY16 and concluded that both the GIST intervention and the control intervention were associated with improved social competence and individual goal attainment. The researchers drafted a consumer brochure, "Social Skills after Traumatic Brain Injury", designed to disseminate their findings to lay persons, and are developing a separate brochure specifically for the military/Veteran population. Additionally, 14 therapists across the country were trained to implement the intervention, expanding the availability of this social competence intervention. A GIST intervention workbook and GIST training is now available from the GIST developers. The findings from this study have a high degree of relevance for returning Service Members and Veterans who have suffered from TBI due to the high prevalence of social reintegration difficulties in this population. The GIST intervention has demonstrated the ability to assist our Service Members and Veterans in returning to full participation in their Families and communities.

### **Trigeminal Sensitization in a Preclinical Model of TBI: Implications for Posttraumatic Headache (PTH)**

It is estimated that nearly a quarter of Service Members wounded in combat during OEF and OIF suffer from TBI. PTH, the most common and persistent symptom of PCS, shares features with migraine headache, such as increased sensitivity of touches to the face and increased sensitivity to light. The changes that underlie PTH, brought on by blast-induced inflammation, are thought to involve the sensitization of the trigeminal pain neural network; however, the precise mechanisms which bring about these changes remain poorly understood. Calcitonin gene-related peptide (CGRP) and nitric oxide (NO) are signaling molecules thought to drive sensitization of the trigeminal pain network following blast injury. In work performed under an FY11 PRMRP Investigator-Initiated Research Award, researchers at Jefferson Medical College utilized a rodent controlled cortical impact (CCI) model to elucidate the respective roles of CGRP and NO in PTH pathophysiology. Blocking CGRP in the trigeminal pain circuit returned mechanical pain sensitivity of CCI rats to levels found in normal rats. In contrast, blocking NO had no effect on mechanical pain sensitivity. Blocking CGRP also decreased the expression of iNOS, one isoform of the enzyme that synthesizes NO, demonstrating that these two molecules mediate PTH pain sensitivity in an interdependent manner. Photosensitivity, a common symptom of PTH, was attenuated in the CCI rodents following inhibition of either CGRP or NO. CGRP expression levels remained high during inhibition of NO, however, which suggests that CGRP and NO contribute to PTH photosensitivity via independent pathways. These results support the conclusion that both CGRP and NO play important roles in the trigeminal

network sensitization contributing to PTH, but that, while co-modulators of mechanical pain sensitization, they may modulate PTH pain sensitivity independently. Following its ameliorating effects on both mechanical and PTH pain sensitivity, this work suggests that CGRP inhibition is a therapeutic target worth pursuing in the effort to treat PTH. For many Service Members who suffer from PTH, CGRP offers a promising target for developing a treatment that not only relieves pain from PTH but potentially reduces side effects through more effective targeting empowered by a thorough knowledge of the pathways involved in PTH-associated sensitization of the trigeminal pain network.

### **Eye Care-related Clinical Recommendations**

In response to the need for clinical guidance regarding combat eye trauma and TBI-related vision problems, VCE produced the following three consensus-based clinical recommendations: (1) Clinical Recommendation for the Eye Care Provider<sup>145</sup> that has been approved by DHA Tri-Service Specialty Care Advisory Board (TSSCAB) and VA; (2) Care and Rehabilitation of Patients with Visual Field Loss Associated with Traumatic or Acquired Brain Injury that has been approved by DHA (TSSCAB) and is pending VA approval; (3) Care and Rehabilitation of Patients with Oculomotor Dysfunctions Associated with TBI that is currently under review by Tri-Service and VA Stakeholder Service Leads prior to submission for approval by DHA (TSSCAB) and VA.

### **Vision Research Oversight**

In FY16, VCE authored or provided expertise and technical oversight on multiple projects designed to assist in diagnosis and treatment of blast-induced ocular trauma as well as improve training in

skills necessary for handling complex ocular injuries caused by blast.

VCE continues to provide oversight of the Phase II SBIR award for the topic titled “Adapting SmartPhones for Ocular Diagnosis”.<sup>146</sup> The anticipated outcome of this topic is the development of a fully functional yet easily portable slitlamp designed on a smartphone platform that will enable more sophisticated diagnosis of eye injuries and conditions under all levels of communication capability.

In addition, VCE provides oversight of the Phase I SBIR award to Neuroctix Corp. titled “Novel Intraocular Visualization Tool”.<sup>147</sup> The anticipated outcome is a novel surgical tool that will allow retinal surgeons to perform sophisticated retinal surgery despite not having a clear view through the cornea. This is anticipated to improve surgical successes and reduce complications in treating complex ocular trauma such as that consequent to blast.

VCE also provided technical oversight and input for a project being directed by USAMRMC titled “Development of Enhanced Biocompatible Materials for the Repair of Ocular Injuries” that aims to create an ocular patch that can help stabilize an ocular wound for transport to the theater ophthalmologist and beyond.

Additionally, researchers at VCE continued to provide technical requirements and directions for the ongoing development of a high-fidelity ocular trauma mannequin simulator by Massachusetts General Hospital funded by the DMRDP managed by CDMRP. The simulator is intended to provide ophthalmologists with high-fidelity models on which to train, regain, and maintain critical surgical skills necessary to treat complex ocular polytrauma, such as that seen in blast injuries.

VCE continues to collaborate intellectually with civilian academic institutions such as JHU and Vanderbilt University, as well as ARL in order to provide input into the



Photo credit: SrA Tinesse Treadwell/US Air Force

development of advanced and sophisticated trauma modeling and simulation paradigms. These collaborations serve as a mechanism of directing research in the areas where there are gaps in knowledge and allow for development of more effective treatments and diagnostic tools, enhance readiness, and support better care for Service Member and Veteran populations, including blast-related research projects.

### **Quantitative Tractography and Volumetric MRI in Blast and Blunt Force TBI: Predictors of Neurocognitive and Behavioral Outcomes**

The vast majority of TBIs are classified as mild to moderate but a significant proportion of these patients report persistent and sometimes disabling cognitive, psychosocial, and functional symptoms. Although results from animal studies indicate that diffuse white matter injury occurs after even relatively mTBI, traditional clinical neuroimaging is frequently not sensitive



to this type of injury suggesting that newer methods are needed to accurately identify patients with TBI and fully characterize their injuries. Researchers at the VA Medical Center of San Diego, California, received funding from the PH/TBIRP managed by the CDMRP to conduct a clinical study to investigate new neuroimaging techniques to characterize mTBI. The major goal of this project is to investigate whether differences in cognitive outcomes are associated with type of injury (blunt versus blast force injury). In addition, researchers are collecting data in order to assess the ability of DTI to measure alterations in structural integrity of the white matter in the brain and determine if these alterations are associated with injury type, psychosocial symptoms, or clinical outcome. The predictive capability of neuroimaging variables will be explored to identify those at highest risk for poor outcomes. Finally, researchers will seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors to brain integrity, neuropsychological functioning, and neurobehavioral outcome. There is a need for integrative, translational studies to advance the understanding of the mechanisms and effects of TBI subtypes, thereby leading to more effective strategies for improved clinical assessment, intervention, and prognosis of patients with mTBI. Results of this study will provide novel information about the effects of differing mechanisms of injury on various brain regions and may provide information on mechanisms of reorganization that may support recovery from injury. Ultimately, these findings can be used to monitor response to potential treatment therapies in future clinical trials.

## Conclusion

It is an honor for the PCO to share so many accomplishments from across the blast injury research community in FY16. The breadth of research topics and outcomes is truly astounding, and it should inspire confidence among Service Members, their Families, and the general public that major advances are being made to protect each Service Member from potential blast injuries, as well as support the injured throughout their treatment and recovery processes. Collaboration across the community—both domestically and internationally—continues to enhance the knowledge base on the spectrum of blast injuries and leads to evidence-based clinical guidelines, programs, and products for blast injury prevention, mitigation, and treatment. The PCO will continue to support the mission of the EA in coordinating medical research that forms the foundation for the programs and products that target blast injuries. By disseminating information on FY16 accomplishments, the PCO encourages collaboration among the research community and builds confidence in the efforts of the Blast Injury Research Program and its domestic and international partners.





008



CHAPTER 8:  
**WAY FORWARD**

**T**his report to the EA covers key accomplishments of the blast injury research community and the PCO in FY16. In FY17 and beyond, the Blast Injury Research Program will continue to pursue strategies for blast injury prevention, mitigation, and treatment. This chapter covers continuing initiatives that will further research and development objectives; foster collaboration and information sharing between research communities; disseminate critical information; and shape future research priorities to fill knowledge gaps across the entire spectrum of blast injury.

## Ongoing PCO Initiatives in FY16

### DoD Blast Injury Research Governing Board

The PCO plans to establish a standing DoD Blast Injury Research Governing Board with representatives from all DoD stakeholder organizations to serve as the venue for identifying blast injury research needs and sharing plans for future blast injury research. It is anticipated that the governing board will provide a forum for cross service coordination and an oversight mechanism for facilitating collaborations and partnerships across the Services and within the various RDT&E communities; and to be a vehicle for wide dissemination of research knowledge related to blast injury across the various medical, operational, testing and evaluation, and materiel communities within the DoD. The specific objectives include:

- Advise EA on requirements, research gaps, and future research investment
- Coordinate and integrate research efforts in order to understand the mechanism of blast injury and accelerate the translation of research acquired knowledge to development of prevention and treatment strategies
- Address current and future blast injury challenges, such as:

- Understanding the mechanisms of blast-related brain injuries in order to guide protection and treatment strategies
- Ensuring access to historical blast injury research data to the widest possible community in order to support research on current and future blast injury challenges
- Identifying candidate MHS Blast Injury Prevention Standards to support the development of effective blast protection systems for both the mounted and dismounted Service Member
- Facilitating information sharing that encourages collaboration, prevents duplication of effort, and fulfills the objective of the Congressional mandate for a coordinated DoD Blast Injury Research Program.

### DoD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-related Threats

The PCO is in the process of establishing a DoD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-related Threats to encourage collaboration and facilitate cooperative RDT&E programs across the DoD related to human injury models of Service Members. It is expected that this Working Group will help to coalesce fragmented and disparate human modeling and simulation programs and projects to create a coordinated and cohesive DoD effort that will enable a new capability for modeling and simulation of human lethality, injury, and impairment from the entire spectrum of blast threat environments. The Working Group will include representatives from stakeholder organizations across the DoD. The specific goals include:



1. Enable the desired capability to accurately model and simulate human lethality, injury, and impairment in all blast threat environments.
2. Share information about current and planned computational modeling research programs focused on human responses to blast-related threats, promoting the common goal of creating a comprehensive capability for modeling the response of the human body to these threats.
3. Develop a strategic plan incorporating existing and planned models, which will be used to enable a capability to accurately model and simulate human lethality, injury, and impairment in all blast threat environments.
4. Share information about programs, identify opportunities for collaboration, and recommend new efforts to close gaps.

### Japan-US Technical Information Exchange Forum on Blast Injury

The PCO is continuing to expand collaboration opportunities with the National Defense Medical College Japan (NDMC), an organization of the Ministry of Defense, Japan, with the goal of achieving a mutual understanding of Japan and US efforts in blast injury research. Following the successful completion of the first Japan-US Technical Information Exchange Forum on Blast Injury held in June 2016, the PCO in collaboration with the NDMC, the Tokyo University of Agriculture and Technology, USAMRMC, and RDECOM, is planning the second Japan-US Technical Information Exchange Forum on Blast Injury which will be hosted by the NDMC in Tokyo, Japan, in April 2017. The purpose of the Forum is to bring together blast injury researchers and clinicians from the US and Japan to share expertise, experience, and approaches to solving blast injury problems of mutual interest; to identify knowledge gaps; and to identify collaborative research opportunities

that will lead to improvements in prevention, clinical diagnosis, and treatment of blast-related brain, lung, and auditory injuries. Specific topics to be discussed during the FY17 Forum include (1) common data elements, (2) data sharing, (3) clinical studies, (4) blast exposure, (5) behavioral studies, and (6) current knowledge gaps.

### US-India Medical Strategic Initiatives Working Group

The PCO plans to provide EA oversight for the US-India Medical Strategic Initiatives Working Group within the ASBREM COI. The Medical Strategic Initiatives Working Group was established by the Chair of the ASBREM COI to provide guidance, encourage collaboration, and facilitate cooperative medical RDT&E projects between the US and India. The collaborative efforts will be conducted under the umbrella of the Memorandum of Agreement between the US DoD and the Ministry of Defence of the Republic of India for RDT&E Projects. The formation of this Working Group serves to represent the combined medical RDT&E interests of the India-US Joint Technology Group with the goal of promoting partnership and coordination between the US DoD and India's Ministry of Defense. The Medical Strategic Working Group in coordination with DTRA, the Office of the ASD(R&E), and DRDO, Indian Ministry of Defence, is helping to organize joint US-India medical and chemical/biological workshops in the Spring of 2017.

### US-India Collaboration on Experimental and Computational Studies of Blast and Blunt TBI

Under the US-India DTTI, the PCO in collaboration with MOMRP developed, received approval, and secured OSD matching funds for the project titled, "Experimental and Computational Studies of Blast and Blunt Traumatic Brain Injury." The outcome

of this effort will support the rapid design, prototyping, and testing of novel protective and therapeutic concepts that will lead to faster introduction of enhanced protective and treatment strategies. The USAMRMC and INMAS-DRDO (an organization of the Ministry of Defence, India) are the lead collaborative organizations. Other participants include BHS AI, NJIT, NRL, WRAIR, DIPR, and ITBRL. The specific objectives of the project include:

- Develop and validate a blast injury animal model for mTBI using imaging techniques and histological procedures, as well as assessing changes in behavior and cognition
- Develop, validate, and cross-validate a computational model for blast and blunt injury
- Develop anatomically accurate head/brain models for blast /blunt injuries from clinical and experimental data
- Compare the blunt and blast data to develop a scaling ratio.

The kickoff meeting for this project was held in FY16, and initial data collection has commenced across the multiple collaborating organizations.

### Preservation and Dissemination of DoD Historical Blast Bioeffects Injury Data

In support of the EA's responsibility to promote information sharing and dissemination, the PCO continues to support an effort to recover and disseminate historical blast bioeffects research data collected at the Albuquerque Blast Test Site on Kirtland AFB, New Mexico, over a period of nearly five decades, from 1951 to 1998. These data were generated from a range of experiments involving more than 12,000 animal subjects representing 13 species, and a wide spectrum of blast conditions including explosions in the open field, in enclosures, and underwater. Additionally, experiments were done using a variety of blast and shock tubes. Knowledge gained from these data can be used to improve



Photo credit: EJ Hersom/US DoD

Service Member protection, survivability, and warfighting capabilities. The goal of this project is to make the data available to DoD PMs, DoD and DoD-sponsored researchers, and medical decision makers engaged in understanding blast-induced injuries and developing protection technologies.

### NATO HFM-270 (RTG)—Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-related Threats

The HFM-270 (RTG) activities will start with a Kickoff meeting in early October 2017 to be held at the CSO of NATO's STO. At this meeting the TT will put together the Program of Work that will guide this panel over their three year tenure. The topics to be covered include:

- Computational modeling of human lethality, injury, and impairment from blast threats, in both mounted and dismounted scenarios
- Previous, ongoing, and planned blast injury biomedical research and computational modeling efforts, and how these fit into overarching frameworks for understanding mechanisms of injury and development of protective systems
- Identification of the gaps that remain in the mechanisms of blast-related injury and in understanding how to adequately protect from these injuries.

By leveraging previous, ongoing, and planned blast injury biomedical research and computational modeling efforts among the participating nations, the HMF-270 (RTG) will develop a framework for translating scientific information into the capability to model the

mechanisms of human lethality, injury, and impairment across the spectrum of blast-related threats.

### **BIPSR Process**

In the coming year, the PCO plans to finalize recommendations from the BIPSR Process for the Spine and Back and Upper Extremity Blast Injury Types. The S&T knowledge gaps identified for these MHS BIPSR Process Blast Injury Types, as well as the Lower Extremity Blast Injury Type, will be shared with the medical research community to inform the development of future MHS Blast Injury Prevention Standards. The PCO also plans to initiate the BIPSR Process for the Dermal Burns Blast Injury Type. In continuation of efforts to enhance BIPSR Process capabilities, the PCO plans to continue to prove out the iBIPSR capability using the Auditory Blast Injury Type as exemplar. The PCO provided initial iBIPSR site access to the Auditory Focused Stakeholders, with their feedback driving improvements as they engage with the site. The PCO anticipates moving forward with the iBIPSR capability on future BIPSR Process Evaluations, and plans to provide access to relevant Stakeholder communities. In addition, the PCO plans to continue the reprioritization of the remaining MHS BIPSR Process Blast Injury Types with the participation of BIPSR Process Stakeholders. Lessons learned from each MHS BIPSR Process Blast Injury Type evaluation will be applied to refine and enhance the BIPSR Process. Ultimately, the knowledge gaps discovered and the recommendations developed through the BIPSR Process will enable the DoD to apply MHS Blast Injury Prevention Standards that support weapon system health hazard assessments, combat platform occupant survivability assessments, and protection system development and performance testing.

### **Brain Health Research Program**

In FY17, the Brain Health Research Program Coordinator plans to cultivate and build upon established relationships across federal agencies, academic institutions, and industry organizations to facilitate novel TBI research efforts. Through these interactions, the Brain Health Research Program Coordinator anticipates improving communication among TBI researchers, clinicians, and leaders, bringing additional clarity to ongoing neurotrauma/neurodegeneration research and providing a roadmap for both short- and long-term TBI research initiatives. The Brain Health Research Program Coordinator will continue to support the EA responsibility to disseminate information, specifically state of the science of brain trauma research findings and recommendations, through attending scientific conferences, advisory boards, and review panels. The Brain Health Research Program Coordinator will continue working to guide TBI research efforts towards not only precision medicine but also precision research. In addition, the Brain Health Research Program Coordinator plans to improve the current electronic communication platform by leveraging the PCO's public-facing website and increasing the organization's presence on social media. The goal is to create a clearinghouse of information on TBI and associated mental health topics and research findings that will be accessible and informative to researchers, policymakers, and the general public.

### **Ongoing Activities Across the DoD Blast Injury Research Program**

The prevention, mitigation, and treatment of blast injuries cannot be addressed without the cooperative RDT&E efforts of organizations across the DoD, other federal agencies, academia, industry, and international partners. The following are examples of initiatives that will continue to address the challenges of blast injuries in FY17 and beyond.

## US Army Hyperbaric Oxygen Clinical Trial

In 2015-2016, the Hyperbaric Oxygen (HBO2) Project Management Office, USAMMDA completed a HBO2 interventional trial under an IND Application held by the US Army OTSG (IND 104,678). This study, entitled “Brain Injury and Mechanism of Actions (BIMA),” is a FDA-cleared Phase 2 multi-center, placebo-controlled study of low dose oxygen using neurologic and neuroradiologic outcome measures. The study subject population was comprised of active duty military personnel and Veterans.

In a parallel effort, a comparative study, known as the “Normal” study, evaluated the same outcome measures as used in BIMA. The Normal study volunteers consisted of healthy, non-concussed civilians and military personnel (active and inactive), who were followed without instituting a study intervention, thereby generating normative datasets. Accordingly, Normal study outcomes established “normal” values against the BIMA study outcomes.

HBO2 is an intervention in which a patient breathes 100 percent oxygen intermittently inside a chamber pressurized to higher than sea level pressure, specifically pressures of 1.4 atmospheres absolute (ATA) or higher. In keeping with the FDA and Undersea and Hyperbaric Medical Society guidelines, breathing 100 percent oxygen at pressures less than 1.4 ATA or exposing isolated parts of the body rather than the entire body to 100 percent oxygen at pressure does not constitute HBO2 treatment.

The BIMA and Normal studies are a DoD, multi-center, Phase 2 trial conducted at the Outcomes Assessment Center within the Evans Army Community Hospital located in Colorado Springs, Colorado; Laboratory and Radiology at Evans Army Community Hospital at Fort Carson, Colorado; and the recruitment was performed by the Study Coordinating Center at Latter Day Saints

Hospital in Salt Lake City, Utah. The BIMA and Normal study design consisted of two study arms, one at 1.5 ATA pressurization breathing 100 percent oxygen and the other at 1.2 ATA pressurization breathing room air (21 percent oxygen). By study conclusion, the BIMA and Normal studies enrolled 71 and 83 subjects, respectively. Subject interaction and data collection for the studies were completed in January 2016. Data analysis is currently ongoing, with initial outcome results expected the second quarter FY17. Study results are scheduled to be submitted to the FDA in a Clinical Study Report shortly thereafter, with subsequent publication of a series of manuscripts in peer reviewed journals no later than first quarter of FY20. Sixty-six BIMA study subjects, who provided consent for future use of their samples, had specimens accessioned at their study baseline, 13-week, and six-month follow-up visits. Similarly, 83 Normal study subjects provided consent for future use of their blood samples that were accessioned at their study baseline and six months. These samples are currently maintained in a biorepository, which may be used in future studies examining chronic neuro-response biomarkers, plasma- and leukocyte-based markers of TBI, and other molecular techniques, potentially revealing gene, protein, or other macromolecule expressions predictive of or influencing clinical outcomes after TBI. In order to share data across the entire TBI research field and to facilitate collaboration between laboratories, the data will also be submitted into the FITBIR informatics system.

The DoD remains committed to researching and providing evidenced-based solutions for wounded Service Members. Beyond the above, the DoD is actively investigating a number of alternate potential treatments for wounded Service Members for the treatment of PCS and PTSD.



## Brain-Heart Initiative (BHI)

Cardiovascular health is a core concern for military readiness and remains the leading cause of death and morbidity in current and former Service Members. Furthermore, cardiovascular disease is a leading contributor to MHS costs. The two signature injuries of the recent conflicts have been PTSD and TBI—notably mTBI—which results typically from explosive and blast injury.<sup>148,149</sup> There is growing evidence that CVD and elevated cardiovascular risk factors may be long-term consequences of PTSD. On the other hand, mTBI and its physical health consequences, other than effects on psychiatric and neurological function, remain largely unknown. BHI is a multidisciplinary program consisting of three inter-related studies investigating the relationship of PTSD and mTBI to CVD, particularly atherosclerotic cardiovascular disease (ASCVD) and its precursors.

The BHI investigators consist of a unique multidisciplinary group of individuals drawn from the fields of radiology/nuclear medicine, psychology, cardiology, neurology, psychiatry, and physical medicine and rehabilitation. This collaboration promises to provide a unique perspective through utilizing state-of-the-art technologies to study the association between mTBI, PTSD, and CVD.

- Project 1, “Comparison of Cardiovascular Outcomes in Patients with Traumatic Brain Injury,” which is being conducted at the WRNMMC is a retrospective population study investigating the incidence of cardiovascular diagnoses in Service Members with the diagnosis of TBI and/or PTSD versus those without the diagnoses.
- Project 2, “Subclinical Atherosclerotic Cardiovascular Disease and Risk Assessment,” is being conducted at USUHS. It is a comprehensive evaluation of ASCVD using a battery of methods that includes advanced cardiovascular imaging, serum biomarkers, electrocardiogram testing,

autonomic testing, and sleep testing of patients with TBI and/or PTSD compared with those without the diagnoses.

- Project 3, “Myocardial Ischemia during Pharmacological Stress and Myocardial Sympathetic Activation in Patients with PTSD and TBI,” is being conducted at USUHS. This study is an advanced imaging and psychological stress assessment of a subset of patients from Project 2 with TBI/PTSD and who are at high risk for coronary artery disease.

Data collection for all three projects will begin in FY17.

Overall, this research program will elucidate the possible role of stress as a trigger of cardiovascular events among individuals with PTSD and mTBI as well as provide an assessment of chronic changes in cardiac sympathetic function in this process. As returning Service Members survive their initial injuries and successfully undergo physical rehabilitation, heart disease remains a significant health concern. Proper recognition and understanding of the potential roles that the nervous system and brain may play in the development of heart disease in patients who have sustained mTBI and/or PTSD will provide the evidence necessary to develop improved screening and treatment guidelines.

## Military and Civilian Recruitment Protocols at the Center for Neuroscience and Regenerative Medicine (CNRM)

Recruitment of participants for TBI and PTSD clinical research studies is a major challenge, causing delays in study timelines and even study failures. To address this challenge, researchers at CNRM Recruitment Core (<https://www.usuhs.edu/cnrm/core10>) at USUHS developed protocols to facilitate the identification and screening of potential participants for referral to a broad range of TBI and PTSD studies. Military and civilian individuals are eager to participate in screening protocols that support a better

understanding of the impact of TBI and PTSD upon symptoms, neuroimaging findings, neurocognitive performance, and blood biomarkers. Such protocols also facilitate research on TBI by providing a large number of potential enrollees for new clinical studies, for whom considerable data has already been collected that can indicate whether they are likely to be eligible and interested in each study, saving valuable time, and making it more likely that such studies will achieve target enrollment numbers. Participants are recruited from civilian hospitals, MTFs, and through various events and presentations. Enrolled participants are referred to other studies during initial enrollment, follow-up visits, or ad-hoc as new CNRM studies became active. A centralized online database is utilized to streamline the eligibility and referral process. To date, 889 participants have been enrolled through the NIH-based “civilian” protocol, and 228 participants have been enrolled through the more recently established Military Recruitment Protocol. Aside from facilitating enrollment into other CNRM-funded and collaborative clinical trials addressing TBI and PTSD, a wealth of data has also been acquired through their participation in these screening protocols, including structural and resting state fMRI, DTI, the NIH Toolbox Neurocognitive Assessment Battery (NIH Toolbox®),<sup>150</sup> blood samples that have been banked for biomarker assays, and a variety of questionnaire data including the NSI and the PTSD Checklist. Currently, CNRM researchers are beginning to analyze this vast amount of data.

### Powered Prosthetic Knees

Ongoing clinically relevant research focused on advanced prosthetics and orthotics is conducted at the three DoD Advanced Rehabilitation Centers—WRNMMC, CFI, NMCS. For example, preliminary work was conducted at WRNMMC, and accepted for publication in the *Journal of Prosthetics and*

*Orthotics*, investigating the effectiveness of the issuance of a powered prosthetic knee as the first prosthetic device in rehabilitation.<sup>151</sup> The results demonstrated accelerated mobility timelines, over those who were initially issued a microprocessor device. Further work is needed to identify optimal patient selection and timing of fitting for powered prosthetic knees to enhance near-term rehabilitation outcomes, as well as the influences of initial fit with powered technologies on quality of movement over the longer term. Providing a powered prosthetic knee as the first fitted device in early rehabilitation may accelerate mobility timelines and ultimately improve long-term outcomes.

### Topical Administration of P13 Peptide as Ear Drops against Blast-induced Auditory Dysfunction

Blast exposure has been identified as the major cause of TBI and auditory dysfunctions including tinnitus in recent military conflicts. Blast-induced auditory injuries including central auditory processing damage and tinnitus are the most prevalent military service associated disabilities with up to 60 percent of blast injured patients exhibiting hearing loss and tinnitus resulting in a total compensation greater than \$1 billion annually for treatment. So far no effective treatment strategies have been developed. Preliminary findings from a recent study conducted by 13Therapeutics (Portland, Oregon) have shown significant promise of their anti-inflammatory peptide, P13, against noise-induced hearing impairments in mice. P13 applied topically through ear drops was found to cross the intact tympanic membrane and reach the inner ear to prevent hearing impairment after noise exposure. P13 administration as an ear drop was also found to be effective against age-related hearing loss. No studies have been conducted so far to evaluate the efficacy of P13 against blast-induced auditory dysfunction. Currently, researchers at WRAIR are testing the efficacy



of topical administration of P13 as ear drops for protection against blast-induced auditory dysfunction using validated pre-clinical models. In this study, rats are exposed to single BOP waves using an ABS and treated topically with P13 peptide as ear drops at a dose of 10 micrograms per ear (in 30 microliters volume) at one hour post-blast and every 24 hours until the end of the study. The auditory functions are assessed using ABR and Distortion Product Otoacoustic Emission measurements at different intervals post-blast. The study is currently in the data collection phase. By establishing an effective novel route of delivery, these experiments will expand the realm by which auditory and vestibular impairments resulting from blast injuries can be pharmacologically treated.

### Understanding TBI Mechanisms using Proton Radiography and Fluid Structure Interaction

Protecting Service Members from the initial injury of blast TBI has greater potential to improve their lives, as opposed to treating the exceedingly complex injury after it has occurred. Unfortunately, the mechanism of this injury is not understood, thus it is unclear if any of the current countermeasures reduce primary blast injury. The key clinical features of severe blast TBI are subarachnoid hemorrhage, pseudoaneurysm, and severe and almost immediate cerebral edema, all of which require prompt neurosurgical intervention. Large animal studies and pathological reviews of clinical blast TBI data also highlight that the periventricular tissue has a predilection to damage. Interestingly, all of these vulnerable structures are fluid-solid interfaces within the head, thus researchers at the 59th Medical Wing hypothesized that a key component of primary blast injury arises from the interaction of blast waves upon these key intracranial fluid-solid interfaces. Previous

computational and experimental studies have not investigated these interfaces, and animal models have not reliably reproduced the injury seen on the battlefield.

In order to investigate what specific forces cause damage to the vasculature and ventricles, researchers at the 59th Medical Wing in collaboration with the Department of Neurology, San Antonio Military Medical Center, Sandia National Laboratories, Los Alamos National Laboratories, and Department of Mechanical Engineering, Michigan State University have developed a test-object which contains models of vasculature and ventricles, encased in a model skull filled with fluid to represent CSF and blood. Using high speed optical imaging and eventually harnessing other advanced radiography methods (flash x-rays and/or proton radiography), the interface mechanics of these modeled intracranial interfaces will be explicitly captured. After blast, test objects will undergo CT and will be dissected to quantify damage to the vascular and ventricular interfaces. This experimental data will be used in conjunction with the advanced simulation capabilities of Sandia National Laboratories in order to isolate the specific components of the blast wave which cause damage to the fluid-solid interfaces within the test object. Following the initial rounds of testing, new helmet designs will be proposed, tested computationally, and then tested experimentally to demonstrate a reduction of the interface damage within the test object.

Prevention of blast TBI is the best strategy to reduce TBI's detrimental impact on Service Members. This study will result in knowledge that will be critical for developing future improvements in prevention of blast TBI and identifying the Service Members exposed to blast TBI who are at risk for vascular damage. In addition, this study will result in a knowledge product linking mechanical forces





Photo credit: National Intrepid Center of Excellence in Bethesda, Maryland

to the injury of severe human blast TBI. This knowledge product will define engineering metrics that can be used to enhance PPE for future Service Members. Using this information, the research team will develop and test a helmet design to demonstrate that such an approach can reduce intracranial interface damage, ultimately collaborating with an industry partner to manufacture helmet prototypes which can greatly reduce the injury of blast TBI.

### Characterization of the Mechanisms of Blast-induced Brain Injury

Service Member exposure to IEDs is suspected to cause non-impact, blast-induced TBI.<sup>152-155</sup> However, to date, no consensus

exists regarding the existence or the mechanisms of blast-induced TBI.<sup>156</sup> Two competing theories have been proposed to explain the potential physical mechanisms of blast-induced TBI: direct and indirect transmission mechanisms. In the direct mechanism, damage to brain tissues is assumed to result from blast wave interactions with just the head,<sup>157-161</sup> while in the indirect mechanism, damage is assumed to result from a blood surge to the brain from blast-wave interactions with just the torso.<sup>162-165</sup> In previous studies, researchers invariably started with preconceived notions about the specific mechanism (direct or indirect) that causes blast-induced TBI and designed experiments to confirm their premise. Such

an approach unnecessarily assumes that the mechanisms are mutually exclusive and fails to consider multiple, competing effects.

At the DoD BHS AI, a subordinate organization of TATRC of the USAMRMC, Fort Detrick, Maryland, researchers proposed to characterize and quantify the mechanisms that could cause blast-induced TBI; they hypothesize that the effects of blast waves on the brains of rats from the direct and indirect mechanisms can be separately characterized and quantified using high-fidelity computational models, based on and validated with customized shock-tube experiments. To this end, BHS AI researchers propose to: 1) establish brain material properties and develop a high-fidelity computational model of the brain, considering it as a porous material and including vasculature; 2) experimentally validate the high-fidelity brain model and characterize the biomechanical brain-tissue responses due to the direct mechanism; 3) develop and experimentally validate a whole-body computational model, and characterize the brain-tissue responses due to the indirect mechanism; and 4) delineate the contributions from the direct and indirect mechanisms, as well as their combined effects, and identify correlates between predicted biomechanical responses and observed brain-tissue damage.

The above mentioned, ongoing interdisciplinary efforts involve computational modeling and experimental studies, during which customized experiments are being performed to generate data for model development and model validation. Initial findings from this work relating to the direct mechanism have been previously published.<sup>166</sup> Using rat animal models, BHS AI researchers have established brain material properties through experimental studies at the universities of Utah and Maryland to develop high-fidelity

brain-injury FEMs. The study team will expose animals to head-only, torso-only, and whole-body blast waves in shock tubes at the WRAIR and NJIT to characterize and quantify the effects of the direct and indirect mechanisms of injury and to refine and validate the computational models. BHS AI researchers will use the validated models to characterize and quantify the effects of the direct and indirect mechanisms of injury. It is not possible to design protective equipment to prevent and mitigate blast-induced TBI unless the underlying mechanisms of the injury are understood. This effort will provide such critical knowledge, ultimately leading to improved Service Member protection against blast-induced TBI and better treatment strategies for casualties of blast exposure.





APPENDIX A:  
**ACRONYMS**

<b>A</b>			
ABS	Advanced Blast Simulator	ATA	Atmospheres Absolute
ABDS	Active Blast Defense System	ATC	Aberdeen Test Center
ABR	Auditory Brainstem Response	ATD	Anthropomorphic Test Device
ABTD	Anthropomorphic Blast Test Device	ATEC	Army Test and Evaluation Command
ACH	Advanced Combat Helmet	ATLIS	Aeromedical Transport Litter Immobilization and Stabilization
AE	Above Elbow	AUC	Area Under the Curve
AEM	Aeromedical Equipment Module		
AFB	Air Force Base	<b>B</b>	
AFFD WG	Auditory Fitness for Duty Working Group	BADER	Bridging Advanced Developments for Exceptional Rehabilitation
AFIRM	Armed Forces Institute of Regenerative Medicine	BBB	Blood Brain Barrier
AFO	Ankle-foot Orthosis	BBVR	BrightBrainer™ Virtual Reality
AFRL	Air Force Research Laboratory	BCS	Ballistic Combat Shirt
AIS	Abbreviated Injury Scale	BC-PSI	British Columbia Postconcussion Symptom Inventory
ALF	Accelerative Loading Fixture	BE	Below Elbow
ALI	Acute Lung Injury	BHI	Brain-Heart Initiative
APG	Aberdeen Proving Ground	BH&T	Ballistic Hull and Turret
AR	Acute Rejection	BHSAI	Biotechnology High Performance Computing Software Applications Institute
AR2B	Army Resources and Requirements Board	BIPSR	Blast Injury Prevention Standards Recommendation
ARDS	Acute Respiratory Distress Syndrome	BIMA	Brain Injury and Mechanism of Actions
ARL	Army Research Laboratory	BMI	Body Mass Index
ARU	Auditory Risk Unit	BOP	Blast Overpressure
ASA(ALT)	Assistant Secretary of the Army for Acquisition, Logistics, and Technology	BOP-HHA	Blast Overpressure-Health Hazard Assessment
ASBREM	Armed Services Biomedical Research, Evaluation, and Management	BPMN	Business Process Modeling Notation
ASD(HA)	Assistant Secretary of Defense for Health Affairs	BRC	Biofidelity Response Corridor
ASD(R&E)	Assistant Secretary of Defense for Research and Engineering	BTD	Blast Test Device
ASES	Aeromedical Stabilization Evacuation System	BUMED	Bureau of Medicine and Surgery
ASCVD	Atherosclerotic Cardiovascular Disease		



**C**

CAP	Consortium to Alleviate Posttraumatic Stress Disorder
CAPT	US Air Force Captain
CARE	Concussion Assessment, Research, and Education
CBF	Cerebral Blood Flow
CCC	Combat Casualty Care
CCCRP	Combat Casualty Care Research Program
CCI	Controlled Cortical Impact
CCL2	Chemokine Ligand 2
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDMRP	Congressionally Directed Medical Research Programs
CDRH	Center for Devices and Radiological Health
CDST	Clinical Decision Support Tool
CENC	Chronic Effects of Neurotrauma Consortium
CES-D	Center for Epidemiological Studies- Depression Scale
CFD	Computational Fluid Dynamics
CFDRC	CFD Research Corporation
CFI	Center for the Intrepid
CGRP	Calcitonin Gene-Related Protein
CI	Confidence Interval
CIAD	Combat Incident Analysis Division
CIDB	Combat Incident Database
CJCS	Chairman of the Joint Chiefs of Staff
CMS	Comfort Mat System
CNRM	Center for Neuroscience and Regenerative Medicine
CNS	Central Nervous System
COA	Clinical Outcome Assessment
CoE	Center of Excellence
CogSMART	Cognitive Symptom Management and Rehabilitation Therapy
COI	Community of Interest
CPG	Clinical Practice Guidelines

Cpl	US Marine Corps Corporal
CPP	Cryopreserved Platelets
CPT	Cognitive Process Therapy
CPT-II	Continuous Performance Test II
CRADA	Cooperative Research and Development Agreement
CRM	Clinical and Rehabilitative Medicine
CRM RP	Clinical and Rehabilitative Medicine Research Program
CRSR	Center for Rehabilitation Sciences Research
CSF	Cerebrospinal Fluid
CSO	Collaboration Supporting Office
CT	Computed Tomography
CTA	Composite Tissue Allograft
CTE	Chronic Traumatic Encephalopathy
CVD	Cardiovascular Disease
CXCL-2	Chemokine (C-X-C motif) Ligand-2
CXCL-3	Chemokine (C-X-C motif) Ligand-3

**D**

DARPA	Defense Advanced Research Projects Agency
DAS	Data Acquisition System
DASA R&T	Deputy Assistant Secretary of the US Army Research and Technology
DCL	Damage Control Laparotomy
DCO	Damage Control Ophthalmology
DCoE	Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury
DDT	Drug Development Tool
DHA R&D	Defense Health Agency Research and Development
DHCC	Defense Health Clinical Center
DHHS	Department of Health and Human Services
DHP	Defense Health Program
DIPR	Defence Institute of Psychological Research
DME	Durable Medical Equipment

DMRDP	Defense Medical Research and Development Program
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DoDD	Department of Defense Directive
DoDTR	Department of Defense Trauma Registry
DOT	Department of Transportation
DOT&E	Director for Operational Test and Evaluation
DPOAE	Distortion Product Otoacoustic Emission
DRDO	Defence Research and Development Organization
DTI	Diffusion Tensor Imaging
DTIC	Defense Technical Information Center
DTRA	Defense Threat Reduction Agency
DTTI	Defense Trade and Technology Initiative
DVBIC	Defense and Veterans Brain Injury Center
DVEIVR	Defense and Veterans Eye Injury and Vision Registry
DVT	Deep Vein Thrombosis
<b>E</b>	
EA	Executive Agent
EACE	Extremity Trauma and Amputation Center of Excellence
ECGE	Extracorporeal Gas Exchange
EEG	Electroencephalogram
EMED	Expeditionary Medical Encounter Database
ESiT	Environmental Sensors in Training
<b>F</b>	
FDA	US Food and Drug Administration
FDP	Freeze Dried Plasma
FEA	Finite Element Analysis
FEM	Finite Element Model
FITBIR	Federal Interagency Traumatic Brain Injury Research
FFP	Fresh Frozen Plasma

FFRDC	Federally Funded Research and Development Center
fMRI	Functional Magnetic Resonance Imaging
FY	Fiscal Year
<b>G</b>	
GE	General Electric
GFAP	Glial Fibrillary Acidic Protein
GHBMC	Global Human Body Modeling Consortium
GIST	Group Interactive Structured Treatment
<b>H</b>	
H&E	Hematoxylin and Eosin
HAV	Human Acellular Vessel
hBIC	Human Brain Injury Criterion
HBO2	Hyperbaric Oxygen
HBOT	Hyperbaric Oxygen Therapy
HCE	Hearing Center of Excellence
HD	Hemodialysis
HDL	High-Density Lipoprotein
HEMTT	Heavy Expanded Mobility Tactical Truck
HFFD	Hearing Fitness-for-Duty
HFM	Human Factors and Medicine
HIPC	Human Injury Probability Curve
HO	Heterotopic Ossification
HRSPC	Highly Rate-Sensitive Polymer Coating
<b>I</b>	
IARC	Injury Assessment Reference Curve
iBIPSR	Interactive Blast Injury Prevention Standards Recommendation
ICD-9	International Classification of Disease, 9th Revision
ICP	Intracranial Pressure
IDCRP	Infectious Disease Clinical Research Program
IDE	Investigational Device Exemption
IDEO	Intrepid Dynamic Exoskeleton Orthosis

IED	Improvised Explosive Device
IFI	Invasive Fungal Infection
IHPS	Integrated Head Protection System
IIPT	Integrating Integrated Product Team
IL	Interleukin
IMAP	Improved Understanding of Medical and Psychological Needs in Veterans and Service Members with Chronic TBI
IND	Investigational New Drug
INMAS	Institute of Nuclear Medicine and Allied Sciences
INTRuST	The Injury and Traumatic Stress Consortium
IPR	In-Progress Review
I-PREDICT	Incapacitation Prediction for Readiness in Expeditionary Domains
IR	Infrared Thermography
IRB	Institutional Review Board
ISS	Injury Severity Score
I-TAB	Investigating the Neurologic Effects of Training Associated Blast
ITBRL	Indian Terminal Ballistic Research Laboratory

## J

JPC	Joint Program Committee
JHU	Johns Hopkins University
JHU/APL	Johns Hopkins University Applied Physics Laboratory
JIDA	Joint Improvised-Threat Defeat Agency
JIEDDO	Joint Improvised Explosive Device Defeat Organization
JNLWD	Joint Non-Lethal Weapons Directorate
JTAPIC	Joint Trauma Analysis and Prevention of Injury in Combat

## K

KIA	Killed in Action
-----	------------------

## L

LCpl	US Marine Corps Lance Corporal
LDL	Low-Density Lipoprotein
LFT&E	Live Fire Test and Evaluation
LPA	Lysophosphatidic Acid
Lpathomab	LPA antibodies
LPAR	Lysophosphatidic Acid Receptor
LRMC	Landstuhl Regional Medical Center
LSU	Louisiana State University

## M

MAAWS	Multi-Role Anti-Armor/Anti-Personnel Weapon System
MACE	Military Acute Concussion Evaluation
ManTech	Manufacturing Technology
MATDEV	Materiel Development
MAUT	Multi-Attribute Utility Theory
MCP-1	Monocyte Chemotactic Protein-1
MCoE	Maneuver Center of Excellence
MDDT	Medical Device Development Tools
MEDCOM	US Army Medical Command
MEMC	Middle-ear Muscle Contraction
MHS	Military Health System
MHSRS	Military Health System Research Symposium
MIDRP	Military Infectious Disease Research Program
MIL-STD	Military Standard
mRNA	Messenger Ribonucleic Acid
miRNA	Micro Ribonucleic Acid
MIT	Massachusetts Institute of Technology
MMP	Matrix Metalloproteinase
MOM	Military Operational Medicine
MOMRP	Military Operational Medicine Research Program
MPC	Mesenchymal Progenitor Cell

MRAP	Mine Resistant Ambush Protected
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cell
MSgt	US Air Force Master Sergeant
mTBI	Mild Traumatic Brain Injury
MTF	Military Treatment Facility
MTP	Massive Transfusion Protocol

## N

NATO	North Atlantic Treaty Organization
NBRI	Non-Blast-Related Injury
NCAA	National Collegiate Athletic Association
NC-BEST	Neurocognitive Assessment of Blast Exposure Sequela in Training
NDAA	National Defense Authorization Act
NDMC	National Defense Medical College
NEA	Next Evolution Armor
NEW	Net Explosive Weight
NFL	National Football League
NGIC	National Ground Intelligence Center
NHRC	Naval Health Research Center
NICoE	National Intrepid Center of Excellence
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NJIT	New Jersey Institute of Technology
NMCSA	Naval Medical Center San Diego
NMRC	Naval Medical Research Center
NMSG	NATO Modeling and Simulation Group
NO	Nitric Oxide
NRAP	National Research Action Plan
NRL	Naval Research Laboratory
NSRDEC	Natick Soldier Research and Development and Engineering Center

NSWCDD	Naval Surface Warfare Center, Carderock Division
--------	--

## O

OBTT	Operation Brain Trauma Therapy
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ONR	Office of Naval Research
OSD	Office of the Secretary of Defense
OSU	Ohio State University
OTSG	Office of the Surgeon General

## P

PCL-5	Posttraumatic Stress Disorder Checklist-5
PCO	Blast Injury Research Program Coordinating Office
PCS	Post-Concussive Syndrome
PdM HTV	Product Manager Heavy Tactical Vehicle
PE	Pulmonary Embolism
PEO	Program Executive Office
PEO GCS	Program Executive Office Ground Combat System
PEO-STRI	Program Executive Office for Simulation, Training, and Instrumentation
PFC	US Army Private First Class
PH/TBIRP	Psychological Health/Traumatic Brain Injury Research Program
PIHL	Pharmaceutical Interventions for Hearing Loss
PM	Program Manager
PMHS	Postmortem Human Surrogates
POD	Precision Olfactory Delivery
PPE	Personal Protective Equipment
PRMRP	Peer Reviewed Medical Research Program
PRORP	Peer Reviewed Orthopedic Research Program
PSI	Physical Science, Inc.
PTFE	Polytetrafluoroethylene
PTH	Posttraumatic Headache



PTSD	Posttraumatic Stress Disorder
PUFA	Polyunsaturated Fatty Acid

## Q

QOL	Quality of Life
qPCR	Quantitative Polymerase Chain Reaction

## R

RDECOM	Research, Development, and Engineering Command
RDT&E	Research, Development, Testing, and Evaluation
REC	Regional Education Coordinator
RFI	Request for Information
RNA	Ribonucleic Acid
RPQ	Rivermead Postconcussive Symptom Questionnaire
RS	Raman Spectroscopy
RTD	Return to Duty
RTG	Research Task Group

## S

S&T	Science and Technology
SBIR	Small Business Innovation Research
SC2i	Surgical Critical Care Initiative
SCI	Spinal Cord Injury
SCORE	Study of Cognitive Rehabilitative Effectiveness
SECARMY	Secretary of the Army
SECDEF	Secretary of Defense
SF36	36-item Short Form Health Survey
SFC	US Army Sergeant First Class
SGT	US Army Sergeant
SIF	Stress Intensity Factor
SLAD	Survivability/Lethality Analysis Directorate
SMART	Strategic Memory and Reasoning Training
SMART-CPT	Combination of Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) and Cognitive Processing Therapy (CPT)

SMAW	Shoulder-launched Multipurpose Assault Weapon
SME	Subject Matter Expert
SoD	Strength of Design
SoS	State-of-the-Science
SPC	US Army Specialist
SPS	Soldier Protection System
SrA	US Air Force Senior Airman
SSB	Soldier System Branch
SSG	US Army Senior Sergeant
SSgt	US Air Force/US National Guard Staff Sergeant
STO	Science and Technology Organization
STRONG STAR	South Texas Research Organizational Network Guiding Studies on Trauma and Resilience

## T

<sup>99m</sup> Tc	Technetium-99m
T2	National Center for Telehealth and Technology
T&E	Testing and Evaluation
TAC	Traumatic Brain Injury Advisory Committee
TARDEC	US Army Tank Automotive Research Development and Engineering Center
TATRC	Telemedicine and Advanced Technology Research Center
TBI	Traumatic Brain Injury
TBI-CDE	TBI Common Data Elements
TCRD	Test Capability Requirements Document
TD	Technology Demonstrator
TDAP	Tissue Data and Acquisition Protocol
TDP	Technical Data Package
TEC-D/STO	Technology Enabled Capability Demonstration/Science and Technology Objective
TED	Traumatic Brain Injury Endpoints Development
TEF	Toxic Embedded Fragment

TIDOS	Trauma Infectious Disease Outcomes Study
TIMP-1	Tissue Inhibitors of Metalloproteinase 1
TNF- $\alpha$	Tumor Necrosis Alpha
TOTSL	Tri-Service Ocular Trauma Skills Laboratory
TRACK-TBI	Transforming Research and Clinical Knowledge in Traumatic Brain Injury
TRADOC	US Army Training and Doctrine Command
TSgt	US Air Force Technical Sergeant
TSWG	Technical Support Working Group
TT	Technical Team

## U

UBB	Under-body Blast
US	United States
USAARL	US Army Aeromedical Research Laboratory
USACEHR	US Army Center for Environmental Health Research
USAISR	US Army Institute of Surgical Research
USAMMDA	US Army Medical Materiel Development Activity
USAMRMC	US Army Medical Research and Materiel Command
USARIEM	US Army Research Institute of Environmental Medicine
USD(AT&L)	Under Secretary of Defense for Acquisition, Technology, and Logistics
USSOCOM	US Special Operations Command
USUHS	Uniformed Services University of the Health Sciences
UVA	University of Virginia

## V

VA	US Department of Veterans Affairs
VC	Vehicle Commander
VCA	Vascularized Composite Allotransplantation
VCE	Vision Center of Excellence
VCU	Virginia Commonwealth University
VRP	Vision Research Program
VRS	Visible Reflectance Spectroscopy
VT	Virginia Polytechnic University and State University
VTE	Venous Thromboembolism

## W

WIA	Wounded in Action
WIAMan	Warrior Injury Assessment Manikin
WII	Wounded, Ill, and Injured
WEO	Warrior Injury Assessment Manikin Engineering Office
WFU	Wake Forest University
WRAIR	Walter Reed Army Institute of Research
WRNMMC	Walter Reed National Military Medical Center
WSU	Wayne State University
WWRP	Wounded Warrior Recovery Project



APPENDIX B:  
**REFERENCES**

1. Collins, S. (2016). Airman Earns “Ultimate Champion” Title at Warrior Games. Retrieved from <http://www.af.mil/News/ArticleDisplay/tabid/223/Article/808489/airman-earns-ultimate-champion-title-at-warrior-games.aspx>
2. Institute of Medicine (US) Committee on Gulf War and Health: Brain Injury in Veterans and Long-Term Health Outcomes. Washington (DC): National Academies Press (US); 2008.
3. Enhancing Security and Stability in Afghanistan. (2015). (Report to Congress). Retrieved from [https://www.defense.gov/Portals/1/Documents/pubs/1225\\_Report\\_Dec\\_2015\\_-\\_Final\\_20151210.pdf](https://www.defense.gov/Portals/1/Documents/pubs/1225_Report_Dec_2015_-_Final_20151210.pdf)
4. McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., ... Gordon, W. A. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathologica*, 131(1), 75–86. <https://doi.org/10.1007/s00401-015-1515-z>
5. Raymont, V., Salazar, A., Krueger, F., & Grafman, J. (2011). “Studying Injured Minds” – The Vietnam Head Injury Study and 40 Years of Brain Injury Research. *Frontiers in Neurology*, 2, 15. <https://doi.org/10.3389/fneur.2011.00015>
6. Elder, G. A., Dorr, N. P., De Gasperi, R., Gama Sosa, M. A., Shaughnessy, M. C., Maudlin-Jeronimo, E., ... Ahlers, S. T. (2012). Blast exposure induces post-traumatic stress disorder-related traits in a rat model of mild traumatic brain injury. *Journal of Neurotrauma*, 29(16), 2564–2575. <https://doi.org/10.1089/neu.2012.2510>
7. Helmick, K. M., Spells, C. A., Malik, S. Z., Davies, C. A., Marion, D. W., & Hinds, S. R. (2015). Traumatic brain injury in the US military: epidemiology and key clinical and research programs. *Brain Imaging and Behavior*, 9(3), 358–366. <https://doi.org/10.1007/s11682-015-9399-z>
8. IOM (Institute of Medicine). (2014). *Gulf War and health, volume 9: Long-term effects of blast exposures*. Washington, DC: National Academies Press.
9. Warden, D. (2006). Military TBI during the Iraq and Afghanistan wars. *The Journal of Head Trauma Rehabilitation*, 21(5), 398–402.
10. Moore, D. F., Radovitzky, R. A., Shupenko, L., Klinoff, A., Jaffee, M. S., & Rosen, J. M. (2008). Blast physics and central nervous system injury. *Future Neurology*, 3(3), 243–250. <https://doi.org/10.2217/14796708.3.3.243>
11. Ling, G., Ecklund, J. M., & Bandak, F. A. (2015). Brain injury from explosive blast: description and clinical management. *Handbook of Clinical Neurology*, 127, 173–180. <https://doi.org/10.1016/B978-0-444-52892-6.00011-8>
12. Defense Center of Excellence (DCoE) Annual Reports. [http://www.dcoe.mil/About\\_DCoE/Annual\\_Reports.aspx](http://www.dcoe.mil/About_DCoE/Annual_Reports.aspx)
13. Defense Center of Excellence (DCoE) Centers Page. [http://www.dcoe.mil/About\\_DCoE/Centers.aspx](http://www.dcoe.mil/About_DCoE/Centers.aspx)
14. Defense and Veterans Brain Injury Center (DVBIC) Annual Reports: <http://dvbic.dcoe.mil/about-dvbic>
15. Salazar, A.M., Zitnay, G.A., Warden, D.L., & Schwab, K.A. (2000). Defense and Veterans Head Injury Program: Background and overview. *Journal of Head Trauma Rehabilitation*, 15(5), 1081-1091.
16. Defense and Veterans Brain Injury Center (DVBIC) timeline (approved by leadership but not on website yet — PDF/more content available if needed)
17. Defense and Veterans Brain Injury Center (DVBIC) Clinical Tools Page <http://dvbic.dcoe.mil/resources/clinical-tools>
18. National Research Action Plan (NRAP). 2013. [https://obamawhitehouse.archives.gov/sites/default/files/uploads/nrap\\_for\\_eo\\_on\\_mental\\_health\\_august\\_2013.pdf](https://obamawhitehouse.archives.gov/sites/default/files/uploads/nrap_for_eo_on_mental_health_august_2013.pdf)
19. Defense and Veterans Brain Injury Center (DVBIC) Full List of Publications. <http://dvbic.dcoe.mil/research/browse/dvbic-publications>



20. Bjork, J. M., Burroughs, T. K., Franke, L. M., Pickett, T. C., Johns, S. E., Moeller, F. G., & Walker, W. C. (2016). Laboratory impulsivity and depression in blast-exposed military personnel with post-concussion syndrome. *Psychiatry Research*, 246, 321–325. <https://doi.org/10.1016/j.psychres.2016.10.008>
21. Finkel, A. G., Yerry, J. A., Klaric, J. S., Ivins, B. J., Scher, A., & Choi, Y. S. (2016). Headache in military service members with a history of mild traumatic brain injury: A cohort study of diagnosis and classification. *Cephalalgia : An International Journal of Headache*. <https://doi.org/10.1177/0333102416651285>
22. Franke, L. M., Walker, W. C., Hoke, K. W., & Wares, J. R. (2016). Distinction in EEG slow oscillations between chronic mild traumatic brain injury and PTSD. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, 106, 21–29. <https://doi.org/10.1016/j.ijpsycho.2016.05.010>
23. O’Neil, M. E., Callahan, M., Carlson, K. F., Roost, M., Laman-Maharg, B., Twamley, E. W., ... Storzbach, D. (2016). Postconcussion symptoms reported by Operation Enduring Freedom/Operation Iraqi Freedom veterans with and without blast exposure, mild traumatic brain injury, and posttraumatic stress disorder. *Journal of Clinical and Experimental Neuropsychology*, 1–10. <https://doi.org/10.1080/13803395.2016.1232699>
24. H.R.5122- John Warner National Defense Authorization Act for Fiscal Year 2007. 109th Congress. <https://www.congress.gov/bill/109th-congress/house-bill/5122/text>
25. Moore, D. F., Radovitzky, R. A., Shupenko, L., Klinoff, A., Jaffee, M. S., & Rosen, J. M. (2008). Blast physics and central nervous system injury. *Future Neurology*, 3(3), 243-250. doi: 10.2217/14796708.3.3.243
26. Ravin, R., Blank, P. S., Brusse, B., Ravin, N., Vira, S., Bezrukov, L., Waters, H., ... Zimmerberg, J. (2016). Blast shockwaves propagate CA2+ activity via purinergic astrocyte networks in human central nervous system cells. *Scientific Reports*, 6, 25713. doi: 10.1038/srep25713
27. Shannahan, L., Weerasooriya, T., Gunnarsson, A., Sanborn, B., & Lamberson, L. (2015). Rate-dependent fracture modes in human femoral cortical bone. *International Journal of Fracture*, 194(2), 81–92. <https://doi.org/10.1007/s10704-015-0035-0>
28. Sanborn, B., Gunnarsson, C. A., Foster, M., & Weerasooriya, T. (2016). Quantitative Visualization of Human Cortical Bone Mechanical Response: Studies on the Anisotropic Compressive Response and Fracture Behavior as a Function of Loading Rate. *Experimental Mechanics*, 56(1), 81–95. <https://doi.org/10.1007/s11340-015-0060-y>
29. Department of Defense Design Criteria Standard Noise Limits. MIL-STD-1474E. (2015) <https://www.arl.army.mil/www/pages/343/MIL-STD-1474E-Final-15Apr2015.pdf>
30. JTAPIC Product 15-072S “Analysis of Fragment Related Injuries” <https://jtapic.arl.army.mil/jacs/pl/product.php?id=431&order=datedesc&filter=published>
31. Bauman, R. A., Ling, G., Tong, L., Januszkiewicz, A., Agoston, D., Delanerolle, N., ... Parks, S. (2009). An introductory characterization of a combat-casualty-care relevant swine model of closed head injury resulting from exposure to explosive blast. *Journal of Neurotrauma*, 26(6), 841–860. <https://doi.org/10.1089/neu.2008.0898>
32. Long, J. B., Bentley, T. L., Wessner, K. A., Cerone, C., Sweeney, S., & Bauman, R. A. (2009). Blast overpressure in rats: recreating a battlefield injury in the laboratory. *Journal of Neurotrauma*, 26(6), 827–840. <https://doi.org/10.1089/neu.2008.0748>
33. VanAlbert, S. A., Ritzel, D. V., & Long, J. B. (2016). Blast Induced Motion from Diffraction-Phase Loading. Presented at the 24th International Symposium on Military Aspects of Blast and Shock (MABS24), Halifax NS, Canada.
34. Bailoor, S., Bhardwaj, R., & Nguyen, T. D. (2015). Effectiveness of eye armor during blast loading. *Biomechanics and Modeling in Mechanobiology*, 14(6), 1227–1237. <https://doi.org/10.1007/s10237-015-0667-z>

35. Bhardwaj, R., Ziegler, K., Seo, J. H., Ramesh, K. T., & Nguyen, T. D. (2014). A computational model of blast loading on the human eye. *Biomechanics and Modeling in Mechanobiology*, 13(1), 123–140. <https://doi.org/10.1007/s10237-013-0490-3>
36. Mader, T. H., Carroll, R. D., Slade, C. S., George, R. K., Ritchey, J. P., & Neville, S. P. (2006). Ocular war injuries of the Iraqi Insurgency, January-September 2004. *Ophthalmology*, 113(1), 97–104. <https://doi.org/10.1016/j.ophtha.2005.07.018>
37. Scott, R. (2010). The injured eye. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 366(1562), 251. <https://doi.org/10.1098/rstb.2010.0234>
38. Adams, G. L. (2004). Combat Eye Protection, the FY 2005 Rapid Fielding Initiative (RFI), and the Approved Product List (APL). United States Army Medical Department.
39. Gondusky, J. S., & Reiter, M. P. (2005). Protecting military convoys in Iraq: an examination of battle injuries sustained by a mechanized battalion during Operation Iraqi Freedom II. *Military Medicine*, 170(6), 546–549.
40. Hilber, D. J. (2011). Eye injuries, active component, U.S. Armed Forces, 2000-2010. *MSMR*, 18(5), 2–7.
41. Cockerham, G. C., Rice, T. A., Hewes, E. H., Cockerham, K. P., Lemke, S., Wang, G., ... Zumhagen, L. (2011). Closed-eye ocular injuries in the Iraq and Afghanistan wars. *The New England Journal of Medicine*, 364(22), 2172–2173. <https://doi.org/10.1056/NEJMc1010683>
42. Mohan, K., Kecova, H., Hernandez-Merino, E., Kardon, R. H., & Harper, M. M. (2013). Retinal ganglion cell damage in an experimental rodent model of blast-mediated traumatic brain injury. *Investigative Ophthalmology & Visual Science*, 54(5), 3440–3450. <https://doi.org/10.1167/iovs.12-11522>
43. Hines-Beard, J., Marchetta, J., Gordon, S., Chaum, E., Geisert, E. E., & Rex, T. S. (2012). A mouse model of ocular blast injury that induces closed globe anterior and posterior pole damage. *Experimental Eye Research*, 99, 63–70. <https://doi.org/10.1016/j.exer.2012.03.013>
44. Wang, H.-C. H., Choi, J.-H., Greene, W. A., Plamper, M. L., Cortez, H. E., Chavko, M., ... Johnson, A. J. (2014). Pathophysiology of blast-induced ocular trauma with apoptosis in the retina and optic nerve. *Military Medicine*, 179(8 Suppl), 34–40. <https://doi.org/10.7205/MILMED-D-13-00504>
45. Sundaramurthy, A. G., Unnikrishnan, G., Mao, H., Williams, T. H., & Reifman, J. (2016). Assessment of the effectiveness of eyewear against blast-induced eye injury. Presented at the Personal Armour Systems Symposium, Amsterdam, Netherlands.
46. Defense Information School. “3rd Place Internal/Public Information: Shields Save Sight.” Online video clip. YouTube. 12 May 2016. <https://www.youtube.com/watch?v=5WugOPoQT1w>
47. Defense Media Activity. (2015). Visual Information Production Award Winners. <http://www.dinfos.dma.mil/Portals/66/Documents/About/Awards/VIPA%202015%20Winners.pdf>
48. Defense Media Activity. Defense Media Awards. <http://www.dma.mil/Services/Defense-Media-Awards/>
49. National Association of Emergency Medical Technicians. TCCC-MP Guidelines and Curriculum. [https://www.naemt.org/education/TCCC/guidelines\\_curriculum](https://www.naemt.org/education/TCCC/guidelines_curriculum)
50. Mazzoli, R. A. (2016). Rigid eye shields to mitigate eye injuries at the Point of Injury (POI). Presented at the A Gathering of Eagles Annual Scientific Symposium of Emergency Medical Systems, Dallas, TX.
51. Nathan, D. E., Bellgowan, J. F., Oakes, T. R., French, L. M., Nadar, S. R., Sham, E. B., ... Riedy, G. (2016). Assessing Quantitative Changes in Intrinsic Thalamic Networks in Blast and Nonblast Mild Traumatic Brain Injury: Implications for Mechanisms of Injury. *Brain Connectivity*, 6(5), 389–402. <https://doi.org/10.1089/brain.2015.0403>
52. Tannous, O., Griffith, C., O’Toole, R. V., & Pellegrini, V. D. J. (2011). Heterotopic ossification after extremity blast amputation in a Sprague-Dawley rat animal model. *Journal of Orthopaedic Trauma*, 25(8), 506–510. <https://doi.org/10.1097/BOT.0b013e31821f6265>

53. Jaffe, D. E., Yoo, D., Blevins, J., Gasbarro, G., Hughes, T., Paryavi, E., ... Pellegrini, V. D. J. (2015). Does Blast Medium Affect Heterotopic Ossification in a Blast-amputation Model? *Clinical Orthopaedics and Related Research*, 473(8), 2680–2687. <https://doi.org/10.1007/s11999-015-4320-z>
54. Bhomia, M., Balakathiresan, N. S., Wang, K. K., Papa, L., & Maheshwari, R. K. (2016). A Panel of Serum MiRNA Biomarkers for the Diagnosis of Severe to Mild Traumatic Brain Injury in Humans. *Scientific Reports*, 6, 28148. <https://doi.org/10.1038/srep28148>
55. Chandran, R., Sharma, A., Bhomia, M., Balakathiresan, N. S., Knollmann-Ritschel, B. E., & Maheshwari, R. K. (2016). Differential expression of microRNAs in the brains of mice subjected to increasing grade of mild traumatic brain injury. *Brain Injury*, 1–14. <https://doi.org/10.1080/02699052.2016.1213420>
56. Balakathiresan, N., Bhomia, M., Chandran, R., Chavko, M., McCarron, R. M., & Maheshwari, R. K. (2012). MicroRNA let-7i is a promising serum biomarker for blast-induced traumatic brain injury. *Journal of Neurotrauma*, 29(7), 1379–1387. <https://doi.org/10.1089/neu.2011.2146>
57. Sharma, A., Chandran, R., Barry, E. S., Bhomia, M., Hutchison, M. A., Balakathiresan, N. S., ... Maheshwari, R. K. (2014). Identification of serum microRNA signatures for diagnosis of mild traumatic brain injury in a closed head injury model. *PloS One*, 9(11), e112019. <https://doi.org/10.1371/journal.pone.0112019>
58. Michael, A. P., Stout, J., Roskos, P. T., Bolzenius, J., Gfeller, J., Mogul, D., & Bucholz, R. (2015). Evaluation of Cortical Thickness after Traumatic Brain Injury in Military Veterans. *Journal of Neurotrauma*, 32(22), 1751–1758. <https://doi.org/10.1089/neu.2015.3918>
59. Gfeller, J. D., & Roskos, P. T. (2013). A comparison of insufficient effort rates, neuropsychological functioning, and neuropsychiatric symptom reporting in military veterans and civilians with chronic traumatic brain injury. *Behavioral Sciences & the Law*, 31(6), 833–849. <https://doi.org/10.1002/bsl.2084>
60. Wang, Y., Wei, Y., Oguntayo, S., Wilder, D., Tong, L., Su, Y., ... Long, J. B. (2016). Cerebrospinal Fluid Chemokine (C-C Motif) Ligand 2 Is an Early-Response Biomarker for Blast-Overpressure-Wave-Induced Neurotrauma in Rats. *Journal of Neurotrauma*. <https://doi.org/10.1089/neu.2016.4465>
61. Li, C., Wu, P., Wu, Z., Limnusun, K., Mehan, N., Mozayan, C., ... Narayan, R. K. (2015). Highly accurate thermal flow microsensors for continuous and quantitative measurement of cerebral blood flow. *Biomedical Microdevices*, 17(5), 87. <https://doi.org/10.1007/s10544-015-9992-3>
62. Li, C., Limnusun, K., Wu, Z., Amin, A., Narayan, A., Golanov, E. V., ... Narayan, R. K. (2016). Single probe for real-time simultaneous monitoring of neurochemistry and direct-current electrocorticography. *Biosensors & Bioelectronics*, 77, 62–68. <https://doi.org/10.1016/j.bios.2015.09.021>
63. Li, C., Wu, Z., Limnusun, K., Cheyuo, C., Wang, P., Ahn, C. H., ... Hartings, J. A. (2016). Development and application of a microfabricated multimodal neural catheter for neuroscience. *Biomedical Microdevices*, 18(1), 8. <https://doi.org/10.1007/s10544-016-0034-6>
64. Li, C., Narayan, R. K., Wu, P.-M., Rajan, N., Wu, Z., Mehan, N., ... Hartings, J. A. (2016). Evaluation of microelectrode materials for direct-current electrocorticography. *Journal of Neural Engineering*, 13(1), 16008. <https://doi.org/10.1088/1741-2560/13/1/016008>
65. Li, C., Chaung, W., Mozayan, C., Chabra, R., Wang, P., & Narayan, R. K. (2016). A New Approach for On-Demand Generation of Various Oxygen Tensions for In Vitro Hypoxia Models. *PloS One*, 11(5), e0155921. <https://doi.org/10.1371/journal.pone.0155921>
66. Wu, Z., Li, C., Hartings, J. A., Narayan, R., & Ahn, C. (2016). Polysilicon Thin Film Developed on Flexible Polyimide for Biomedical Applications. *Journal of Microelectromechanical Systems*, 25(4), 585–592. <https://doi.org/10.1109/JMEMS.2016.2554358>

67. Krueger, B., York, J., Mahoney, E. J., Dreier, J. P., Zuccarello, M., & Hartings, J. A. (2016). Subarachnoid hemorrhage induces spreading depolarizations and cortical infarction. Presented at the Annual Meeting of the American Academy of Neurological Surgeons.
68. Li, C., Limnusun, K., Golanov, E. V., Ahn, C. H., Narayan, R. K., & Hartings, J. A. (2016). Transient brain temperature elevation as a surrogate indicator of cortical spreading depolarization. Presented at the Annual Meeting of the American Academy of Neurological Surgeons.
69. Godbole, N. J., Kim, N. S., Seefeldt, E. S., Morgenstern, A., Egan, J. A., Coyler, M. H., & Mazzoli, R. A. (2016). Simplified method for rapid field assessment of visual acuity by first responders after ocular injury. Presented at the Military Health System Research Symposium, Kissimmee, FL.
70. Eskridge, S. L., Hill, O., Clouser, M. C., Galarneau, M. R. (2016). The Association of Specific Serious Lower Extremity Injuries with Delayed Amputation. Presented at Military Health Systems Research Symposium. Kissimmee, Kissimmee, Florida.
71. Dahl, S. L. M., Kypson, A. P., Lawson, J. H., Blum, J. L., Strader, J. T., Li, Y., ... Niklason, L. E. (2011). Readily available tissue-engineered vascular grafts. *Science Translational Medicine*, 3(68), 68ra9. <https://doi.org/10.1126/scitranslmed.3001426>
72. Benrashid, E., McCoy, C. C., Youngwirth, L. M., Kim, J., Manson, R. J., Otto, J. C., & Lawson, J. H. (2016). Tissue engineered vascular grafts: Origins, development, and current strategies for clinical application. *Regenerative Medicine*, 99, 13–19. <https://doi.org/10.1016/j.ymeth.2015.07.014>
73. Lawson, J. H., Glickman, M. H., Ilzecki, M., Jakimowicz, T., Jaroszynski, A., Peden, E. K., ... Niklason, L. E. (2016). Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. *Lancet (London, England)*, 387(10032), 2026–2034. [https://doi.org/10.1016/S0140-6736\(16\)00557-2](https://doi.org/10.1016/S0140-6736(16)00557-2)
74. Surgical Critical Care Initiative. (2015a). National and Military Health System Cost Savings from WoundDX. Retrieved from [http://www.sc2i.org/site/assets/files/1039/national\\_and\\_mhs\\_cost\\_savings\\_from\\_woundx-1.pdf](http://www.sc2i.org/site/assets/files/1039/national_and_mhs_cost_savings_from_woundx-1.pdf)
75. Hannon, M., Tadlock, M. D., Melcer, T., Walker, J., Bandle, J., Nieves, K., & Galarneau, M. (2016). Venous thromboembolism after traumatic amputation: an analysis of 366 combat casualties. *The American Journal of Surgery*, 212(2), 230–234. <https://doi.org/10.1016/j.amjsurg.2016.01.031>
76. Fries, C. A., Villamaria, C. Y., Spencer, J. R., Rickard, R. F., Gorantla, V. S., & Davis, M. R. (2016). A Porcine Orthotopic Forelimb Vascularized Composite Allotransplantation Model: Technical Considerations and Translational Implications. *Plastic and Reconstructive Surgery*, 138(3), 461e–71e. <https://doi.org/10.1097/PRS.0000000000002451>
77. Surgical Critical Care Initiative. (2015b). Operational Savings from SC2i MTP Project. Retrieved from [http://www.sc2i.org/site/assets/files/1040/operational\\_savings\\_from\\_sc2i\\_mtp\\_-\\_report\\_-\\_may\\_2015.pdf](http://www.sc2i.org/site/assets/files/1040/operational_savings_from_sc2i_mtp_-_report_-_may_2015.pdf)
78. Rasmussen, T. E., Baer, D. G., & Goolsby, C. (2016). The giving back: Battlefield lesson to national preparedness. *The Journal of Trauma and Acute Care Surgery*, 80(1), 166–167. <https://doi.org/10.1097/TA.0000000000000899>
79. Xydakis, M. S., Mulligan, L. P., Smith, A. B., Olsen, C. H., Lyon, D. M., & Belluscio, L. (2015). Olfactory impairment and traumatic brain injury in blast-injured combat troops: a cohort study. *Neurology*, 84(15), 1559–1567. <https://doi.org/10.1212/WNL.0000000000001475>
80. Zangeneh, T., Coggin, A., Pasternak, J., Ryan, D., Sia, R., & Coyler, M. (2016). From residency to deployment: Impact of live tissue-based ocular trauma training on novice and expert military ophthalmologists. In *Proceedings of the 2016 Military Health Science Research Symposium*. Kissimmee, FL.
81. DeMar, J., Sharrow, K., Hill, M., Berman, J., Oliver, T., & Long, J. (2016). Effects of Primary Blast Overpressure on Retina and Optic Tract in Rats. *Frontiers in Neurology*, 7, 59. <https://doi.org/10.3389/fneur.2016.00059>



82. Kauvar, D. S., Wolf, S. E., Wade, C. E., Cancio, L. C., Renz, E. M., & Holcomb, J. B. (2006). Burns sustained in combat explosions in Operations Iraqi and Enduring Freedom (OIF/OEF explosion burns). *Burns : Journal of the International Society for Burn Injuries*, 32(7), 853–857. <https://doi.org/10.1016/j.burns.2006.03.008>
83. Belenkiy, S. M., Buel, A. R., Cannon, J. W., Sine, C. R., Aden, J. K., Henderson, J. L., ... Chung, K. K. (2014). Acute respiratory distress syndrome in wartime military burns: application of the Berlin criteria. *The Journal of Trauma and Acute Care Surgery*, 76(3), 821–827. <https://doi.org/10.1097/TA.0b013e3182aa2d21>
84. Kochanek, P. M., Bramlett, H. M., Shear, D. A., Dixon, C. E., Mondello, S., Dietrich, W. D., ... Tortella, F. C. (2016). Synthesis of Findings, Current Investigations, and Future Directions: Operation Brain Trauma Therapy. *Journal of Neurotrauma*, 33(6), 606–614. <https://doi.org/10.1089/neu.2015.4133>
85. Shear, D. A., Dixon, C. E., Bramlett, H. M., Mondello, S., Dietrich, W. D., Deng-Bryant, Y., ... Tortella, F. C. (2016). Nicotinamide Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. *Journal of Neurotrauma*, 33(6), 523–537. <https://doi.org/10.1089/neu.2015.4115>
86. Bramlett, H. M., Dietrich, W. D., Dixon, C. E., Shear, D. A., Schmid, K. E., Mondello, S., ... Kochanek, P. M. (2016). Erythropoietin Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. *Journal of Neurotrauma*, 33(6), 538–552. <https://doi.org/10.1089/neu.2015.4116>
87. Dixon, C. E., Bramlett, H. M., Dietrich, W. D., Shear, D. A., Yan, H. Q., Deng-Bryant, Y., ... Kochanek, P. M. (2016). Cyclosporine Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. *Journal of Neurotrauma*, 33(6), 553–566. <https://doi.org/10.1089/neu.2015.4122>
88. Mountney, A., Bramlett, H. M., Dixon, C. E., Mondello, S., Dietrich, W. D., Wang, K. K. W., ... Shear, D. A. (2016). Simvastatin Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. *Journal of Neurotrauma*, 33(6), 567–580. <https://doi.org/10.1089/neu.2015.4130>
89. Browning, M., Shear, D. A., Bramlett, H. M., Dixon, C. E., Mondello, S., Schmid, K. E., ... Kochanek, P. M. (2016). Levetiracetam Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. *Journal of Neurotrauma*, 33(6), 581–594. <https://doi.org/10.1089/neu.2015.4131>
90. Mondello, S., Shear, D. A., Bramlett, H. M., Dixon, C. E., Schmid, K. E., Dietrich, W. D., ... Kochanek, P. M. (2016). Insight into Pre-Clinical Models of Traumatic Brain Injury Using Circulating Brain Damage Biomarkers: Operation Brain Trauma Therapy. *Journal of Neurotrauma*, 33(6), 595–605. <https://doi.org/10.1089/neu.2015.4132>
91. Rasmussen, T. E., & Crowder, A. T. (2016). Synergy in Science and Resources. *Journal of Neurotrauma*, 33(6), 511–512. <https://doi.org/10.1089/neu.2016.29007.ter>
92. Assistant Secretary of Defense. Policy on Analysis of Metal Fragments Removed from Department of Defense Personnel. (2007). <http://www.health.mil/~media/MHS/Policy%20Files/Import/07-029.ashx>
93. Parker, A. C., Jennings, J. A., Bumgardner, J. D., Courtney, H. S., Lindner, E., & Haggard, W. O. (2013). Preliminary investigation of crosslinked chitosan sponges for tailorable drug delivery and infection control. *Journal of Biomedical Materials Research. Part B, Applied Biomaterials*, 101(1), 110–123. <https://doi.org/10.1002/jbm.b.32822>
94. Parker, A. C., Beenken, K. E., Jennings, J. A., Hittle, L., Shirliff, M. E., Bumgardner, J. D., ... Haggard, W. O. (2015). Characterization of local delivery with amphotericin B and vancomycin from modified chitosan sponges and functional biofilm prevention evaluation. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society*, 33(3), 439–447. <https://doi.org/10.1002/jor.22760>
95. Rodriguez, C. J., Tribble, D. R., Murray, C. K., Jessie, E. M., Khan, M., Fleming, M. E., ... Shackelford, S. A. (2016). Invasive Fungal Infection in War Wounds (CPG: 28) (Joint Trauma System Clinical Practice Guideline). Retrieved from [http://www.usaisr.amedd.army.mil/cpgs/Invasive\\_Fungal\\_Infection\\_04\\_Aug\\_2016.pdf](http://www.usaisr.amedd.army.mil/cpgs/Invasive_Fungal_Infection_04_Aug_2016.pdf)

96. Saeed, O., Tribble, D., Biever, K., Kavanaugh, M., & Crouch, H. (2016). Infection Prevention in Combat-Related Injuries (CGP ID:24) (Joint Trauma System Clinical Practice Guideline). Retrieved from [http://www.usaisr.amedd.army.mil/cpgs/Infection\\_Prevention\\_08\\_Aug\\_2016.pdf](http://www.usaisr.amedd.army.mil/cpgs/Infection_Prevention_08_Aug_2016.pdf)
97. Tribble, D. R., Li, P., Warkentien, T. E., Lloyd, B. A., Schnaubelt, E. R., Ganesan, A., ... Murray, C. K. (2016). Impact of Operational Theater on Combat and Noncombat Trauma-Related Infections. *Military Medicine*, 181(10), 1258–1268. <https://doi.org/10.7205/MILMED-D-15-00368>
98. Lewandowski, L. R., Weintrob, A. C., Tribble, D. R., Rodriguez, C. J., Petfield, J., Lloyd, B. A., ... Potter, B. K. (2016). Early Complications and Outcomes in Combat Injury-Related Invasive Fungal Wound Infections: A Case-Control Analysis. *Journal of Orthopaedic Trauma*, 30(3), e93-99. <https://doi.org/10.1097/BOT.0000000000000447>
99. Gilbert, L. J., Li, P., Murray, C. K., Yun, H. C., Aggarwal, D., Weintrob, A. C., & Tribble, D. R. (2016). Multidrug-resistant gram-negative bacilli colonization risk factors among trauma patients. *Diagnostic Microbiology and Infectious Disease*, 84(4), 358–360. <https://doi.org/10.1016/j.diagmicrobio.2015.12.014>
100. White, B. K., Mende, K., Weintrob, A. C., Beckius, M. L., Zera, W. C., Lu, D., ... Murray, C. K. (2016). Epidemiology and antimicrobial susceptibilities of wound isolates of obligate anaerobes from combat casualties. *Diagnostic Microbiology and Infectious Disease*, 84(2), 144–150. <https://doi.org/10.1016/j.diagmicrobio.2015.10.010>
101. Lewis, J. D., Wassermann, E. M., Chao, W., Ramage, A. E., Robin, D. A., & Clauw, D. J. (2012). Central sensitization as a component of post-deployment syndrome. *NeuroRehabilitation*, 31(4), 367–372. <https://doi.org/10.3233/NRE-2012-00805>
102. Heaton, S. M., Weintrob, A. C., Downing, K., Keenan, B., Aggarwal, D., Shaikh, F., ... Wells, J. (2016). Histopathological techniques for the diagnosis of combat-related invasive fungal wound infections. *BMC Clinical Pathology*, 16, 11. <https://doi.org/10.1186/s12907-016-0033-9>
103. Mende, K., Beckius, M. L., Zera, W. C., Yu, X., Li, P., Tribble, D. R., & Murray, C. K. (2016). Lack of doxycycline antimalarial prophylaxis impact on *Staphylococcus aureus* tetracycline resistance. *Diagnostic Microbiology and Infectious Disease*, 86(2), 211–220. <https://doi.org/10.1016/j.diagmicrobio.2016.07.014>
104. Mangum, L. C., Garcia, G. R., & Tribble, D. R. (2016). Biofilm Formation Capacity among *Acinetobacter baumannii* and *Enterococcus* species isolates from Clinical Wound Infections of Injured U.S. Military Personnel. Presented at the Military Health System Research Symposium, Kissimmee, FL.
105. Heitkamp, R., Li, P., & Mende, K. (2016). *Enterococcus* spp. in Extremity Trauma Wounds. Presented at the Military Health System Research Symposium, Kissimmee, FL.
106. Tribble, D. R. (2016). The U.S. Department of Defense Trauma Infectious Disease Outcomes Study (TIDOS). Presented at the 3rd Force Health Protection Congress, Hamburg, Germany.
107. Aldridge Whitehead, J. M., Russell Esposito, E., & Wilken, J. M. (2016). Stair ascent and descent biomechanical adaptations while using a custom ankle-foot orthosis. *Journal of Biomechanics*, 49(13), 2899–2908. <https://doi.org/10.1016/j.jbiomech.2016.06.035>
108. Ranz, E. C., Russell Esposito, E., Wilken, J. M., & Neptune, R. R. (2016). The influence of passive-dynamic ankle-foot orthosis bending axis location on gait performance in individuals with lower-limb impairments. *Clinical Biomechanics (Bristol, Avon)*, 37, 13–21. <https://doi.org/10.1016/j.clinbiomech.2016.05.001>
109. Russell Esposito, E., Choi, H. S., Owens, J. G., Blanck, R. V., & Wilken, J. M. (2015). Biomechanical response to ankle-foot orthosis stiffness during running. *Clinical Biomechanics (Bristol, Avon)*, 30(10), 1125–1132. <https://doi.org/10.1016/j.clinbiomech.2015.08.014>
110. Haight, D. J., Russell Esposito, E., & Wilken, J. M. (2015). Biomechanics of uphill walking using custom ankle-foot orthoses of three different stiffnesses. *Gait & Posture*, 41(3), 750–756. <https://doi.org/10.1016/j.gaitpost.2015.01.001>

111. Harper, N. G., Esposito, E. R., Wilken, J. M., & Neptune, R. R. (2014). The influence of ankle-foot orthosis stiffness on walking performance in individuals with lower-limb impairments. *Clinical Biomechanics* (Bristol, Avon), 29(8), 877–884. <https://doi.org/10.1016/j.clinbiomech.2014.07.005>
112. Russell Esposito, E., Blanck, R. V., Harper, N. G., Hsu, J. R., & Wilken, J. M. (2014). How does ankle-foot orthosis stiffness affect gait in patients with lower limb salvage? *Clinical Orthopaedics and Related Research*, 472(10), 3026–3035. <https://doi.org/10.1007/s11999-014-3661-3>
113. Harper, N. G., Russell, E. M., Wilken, J. M., & Neptune, R. R. (2014). Selective laser sintered versus carbon fiber passive-dynamic ankle-foot orthoses: a comparison of patient walking performance. *Journal of Biomechanical Engineering*, 136(9), 91001. <https://doi.org/10.1115/1.4027755>
114. Krupenevich, R. L., Pruziner, A. L., & Miller, R. H. (2016). Knee Joint Loading during Single-Leg Forward Hopping. *Medicine and Science in Sports and Exercise*. <https://doi.org/10.1249/MSS.0000000000001098>
115. Valerio, I. L., Campbell, P., Sabino, J., Dearth, C. L., & Fleming, M. (2015). The use of urinary bladder matrix in the treatment of trauma and combat casualty wound care. *Regenerative Medicine*, 10(5), 611–622. <https://doi.org/10.2217/rme.15.34>
116. Dearth, C. L., Keane, T. J., Carruthers, C. A., Reing, J. E., Huleihel, L., Ranallo, C. A., ... Badylak, S. F. (2016). The effect of terminal sterilization on the material properties and in vivo remodeling of a porcine dermal biologic scaffold. *Acta Biomaterialia*, 33, 78–87. <https://doi.org/10.1016/j.actbio.2016.01.038>
117. Dearth, C. L., Slivka, P. F., Stewart, S. A., Keane, T. J., Tay, J. K., Londono, R., ... Badylak, S. F. (2016). Inhibition of COX1/2 alters the host response and reduces ECM scaffold mediated constructive tissue remodeling in a rodent model of skeletal muscle injury. *Acta Biomaterialia*, 31, 50–60. <https://doi.org/10.1016/j.actbio.2015.11.043>
118. Sheehan, R. C., Rabago, C. A., Rylander, J. H., Dingwell, J. B., & Wilken, J. M. (2016). Use of Perturbation-Based Gait Training in a Virtual Environment to Address Mediolateral Instability in an Individual With Unilateral Transfemoral Amputation. *Physical Therapy*. <https://doi.org/10.2522/ptj.20150566>
119. Rabago, C. A., Dingwell, J. B., & Wilken, J. M. (2015). Reliability and Minimum Detectable Change of Temporal-Spatial, Kinematic, and Dynamic Stability Measures during Perturbed Gait. *PLoS One*, 10(11), e0142083. <https://doi.org/10.1371/journal.pone.0142083>
120. Bell, E. M., Pruziner, A. L., Wilken, J. M., & Wolf, E. J. (2016). Performance of conventional and X2(R) prosthetic knees during slope descent. *Clinical Biomechanics* (Bristol, Avon), 33, 26–31. <https://doi.org/10.1016/j.clinbiomech.2016.01.008>
121. Sosin, M., Ceradini, D. J., Hazen, A., Levine, J. P., Staffenberg, D. A., Saadeh, P. B., ... Rodriguez, E. D. (2016). Total Face, Eyelids, Ears, Scalp, and Skeletal Subunit Transplant Cadaver Simulation: The Culmination of Aesthetic, Craniofacial, and Microsurgery Principles. *Plastic and Reconstructive Surgery*, 137(5), 1569–1581. <https://doi.org/10.1097/PRS.0000000000002122>
122. Sosin, M., Ceradini, D. J., Hazen, A., Sweeney, N. G., Brecht, L. E., Levine, J. P., ... Rodriguez, E. D. (2016). Total Face, Eyelids, Ears, Scalp, and Skeletal Subunit Transplant Research Procurement: A Translational Simulation Model. *Plastic and Reconstructive Surgery*, 137(5), 845e–54e. <https://doi.org/10.1097/PRS.0000000000002326>
123. Sosin, M., Ceradini, D. J., Levine, J. P., Hazen, A., Staffenberg, D. A., Saadeh, P. B., ... Rodriguez, E. D. (2016). Total Face, Eyelids, Ears, Scalp, and Skeletal Subunit Transplant: A Reconstructive Solution for the Full Face and Total Scalp Burn. *Plastic and Reconstructive Surgery*, 138(1), 205–219. <https://doi.org/10.1097/PRS.0000000000002322>

124. Isaacson, B. M., Potter, B. K., Bloebaum, R. D., Epperson, R. T., Kawaguchi, B. S., Swanson, T. M., & Pasquina, P. F. (2016a). Link Between Clinical Predictors of Heterotopic Ossification and Histological Analysis in Combat-Injured Service Members. *The Journal of Bone & Joint Surgery*, 98(8), 647. <https://doi.org/10.2106/JBJS.15.00895>
125. Isaacson, B. M., Potter, B. K., Bloebaum, R. D., Epperson, R. T., Kawaguchi, B., Swanson, T. M., & Pasquina, P. F. (2016b). Determining the Mineral Apposition Rate of Heterotopic Ossification in Military Healthcare System Patients after Total Joint Replacement: A Case Series. *Bone and Tissue Regeneration Insights*, 7(5517–BTRI–Determining–the–Mineral–Apposition–Rate–of–Heterotopic–Ossification–pdf), 1–5. <https://doi.org/10.4137/BTRI.S38041>
126. Kaufman, K., Miller, E., Kingsbury, T., Esposito, E. R., Wolf, E., Wilken, J., & Wyatt, M. (2016). Reliability of 3D gait data across multiple laboratories. *Gait & Posture*, 49, 375–381. DOI: 10.1016/j.gaitpost.2016.07.075
127. Dye, J. L., Eskridge, S. L., Tepe, V., Clouser, M. C., & Galarneau, M. (2016). Characterization and Comparison of Combat-Related Injuries in Women During OIF and OEF. *Military Medicine*, 181(1 Suppl), 92–98. <https://doi.org/10.7205/MILMED-D-15-00237>
128. Dye, J. L., Eskridge, S. L., Clouser, M. C., & Galarneau, M. R. (2014). Characterization and Comparison of Combat-Related Injuries in Women During OIF and OEF. Presented at the Military Health System Research Symposium, Fort Lauderdale, FL.
129. Bhatnagar V., Richard E., Melcer T., Walker J., Galarneau M.R. (2016). Increased prevalence of metabolic syndrome among combat veterans with lower limb amputation. Presented at the Academic Research Conference, San Diego, CA.
130. Walker J., Melcer T., Bhatnagar V., Richard E., Galarneau M.R. (2016). Five-Year Health Care Utilization Trends Following Combat Amputation. Presented at the Military Health Systems Research Symposium. Kissimmee, Florida.
131. Bhatnagar, V., Richard, E., Melcer, T., Walker, J., & Galarneau, M. (2015). Lower-limb amputation and effect of posttraumatic stress disorder on Department of Veterans Affairs outpatient cost trends. *Journal of Rehabilitation Research and Development*, 52(7), 827–838. <https://doi.org/10.1682/JRRD.2014.11.0288>
132. King, R., Lu, L., Williams, R. W., & Geisert, E. E. (2015). Transcriptome networks in the mouse retina: An exon level BXD RI database. *Molecular Vision*, 21, 1235–1251.
133. Struebing, F. L., Lee, R. K., Williams, R. W., & Geisert, E. E. (2016). Genetic Networks in Mouse Retinal Ganglion Cells. *Frontiers in Genetics*, 7, 169. <https://doi.org/10.3389/fgene.2016.00169>
134. Riedy, G., Senseney, J. S., Liu, W., Ollinger, J., Sham, E., Krapiva, P., ... Oakes, T. R. (2015). Findings from Structural MR Imaging in Military Traumatic Brain Injury. *Radiology*, 279(1), 207–215. <https://doi.org/10.1148/radiol.2015150438>
135. Yeh, P.-H., Guan Koay, C., Wang, B., Morissette, J., Sham, E., Senseney, J., ... Ollinger, J. (2016). Compromised Neurocircuitry in Chronic Blast-Related Mild Traumatic Brain Injury. *Human Brain Mapping*. <https://doi.org/10.1002/hbm.23365>
136. Elder, G. A., Dorr, N. P., De Gasperi, R., Gama Sosa, M. A., Shaughnessy, M. C., Maudlin-Jeronimo, E., ... Ahlers, S. T. (2012). Blast exposure induces post-traumatic stress disorder-related traits in a rat model of mild traumatic brain injury. *Journal of Neurotrauma*, 29(16), 2564–2575. <https://doi.org/10.1089/neu.2012.2510>
137. Gondusky, J. S., & Reiter, M. P. (2005). Protecting military convoys in Iraq: an examination of battle injuries sustained by a mechanized battalion during Operation Iraqi Freedom II. *Military Medicine*, 170(6), 546–549.
138. Shively, S. B., Horkayne-Szakaly, I., Jones, R. V., Kelly, J. P., Armstrong, R. C., & Perl, D. P. (2016). Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series. *The Lancet. Neurology*, 15(9), 944–953. [https://doi.org/10.1016/S1474-4422\(16\)30057-6](https://doi.org/10.1016/S1474-4422(16)30057-6)



139. Gattu, R., Akin, F. W., Cacace, A. T., Hall, C. D., Murnane, O. D., & Haacke, E. M. (2016). Vestibular, balance, microvascular and white matter neuroimaging characteristics of blast injuries and mild traumatic brain injury: Four case reports. *Brain Injury*, 30(12), 1501–1514. <https://doi.org/10.1080/02699052.2016.1219056>
140. Eliason, D., White, H.A., & Leatherwood, R. K. (2016). Clinical outcomes of open globe injuries in the Defense and Veterans Eye Injury and Vision Registry. In Proceedings of the 2016 Annual Meeting of the American Academy of Ophthalmology. <https://aao.scientificposters.com/epsAbstractAAO.cfm?id=4>
141. Munoz-Castaneda, J. R., Montilla, P., Padillo, F. J., Bujalance, I., Munoz, M. C., Muntane, J., & Tunez, I. (2006). Role of serotonin in cerebral oxidative stress in rats. *Acta Neurobiologiae Experimentalis*, 66(1), 1–6.
142. Davis, L. L., Suris, A., Lambert, M. T., Heimberg, C., & Petty, F. (1997). Post-traumatic stress disorder and serotonin: new directions for research and treatment. *Journal of Psychiatry & Neuroscience : JPN*, 22(5), 318–326.
143. Gardner, A., & Boles, R. G. (2011). Beyond the serotonin hypothesis: mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 35(3), 730–743. <https://doi.org/10.1016/j.pnpbp.2010.07.030>
144. Walker, M. S., Kaimal, G., Koffman, R., & DeGraba, T. J. (2016). Art therapy for PTSD and TBI: A senior active duty military service member's therapeutic journey. *The Arts in Psychotherapy*, 49, 10–18. <https://doi.org/10.1016/j.aip.2016.05.015>
145. Vision Center of Excellence. Clinical recommendation for the eye care provider: Eye and vision care following blast exposure and/or possible traumatic brain injury. <http://vce.health.mil/Resources/Products/Additional-Resources>
146. Adapting SmartPhones for Ocular Diagnosis. <https://www.sbir.gov/sbirsearch/detail/374127>
147. Novel Intraocular Visualization Tool. <https://www.sbir.gov/sbirsearch/detail/981531>
148. Boscarino, J. A. (2012). PTSD is a risk factor for cardiovascular disease: time for increased screening and clinical intervention. *Preventive Medicine*, 54(5), 363–364; author reply 365. <https://doi.org/10.1016/j.ypmed.2012.01.001>
149. Wentworth, B. A., Stein, M. B., Redwine, L. S., Xue, Y., Taub, P. R., Clopton, P., ... Maisel, A. S. (2013). Post-traumatic stress disorder: a fast track to premature cardiovascular disease? *Cardiology in Review*, 21(1), 16–22. <https://doi.org/10.1097/CRD.0b013e318265343b>
150. U.S. Department of Health and Human Services. NIH Toolbox Neurocognitive Assessment Battery. <http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox>
151. Pasquina, P. F., Carvalho, A., Murphy, I., Johnson, J., Swanson, T., Hendershot, B. D., ... Isaacson, B. M. (2016). A Case Series of Wounded Warriors Receiving Initial Fit PowerKnee Prosthesis., Accepted for Publication.
152. Sollinger, J. M., Fisher, G., & Metscher, K. N. (2008). The Wars in Afghanistan and Iraq- An Overview. In T. Tanielian & L. H. Jaycox (Eds.), *Invisible Wounds of War: Psychological and Cognitive Injuries, their Consequences, and Services to Assist Recovery* (pp. 19–31). Santa Monica, CA: RAND Corporation.
153. Ritenour, A. E., Blackbourne, L. H., Kelly, J. F., McLaughlin, D. F., Pearse, L. A., Holcomb, J. B., & Wade, C. E. (2010). Incidence of primary blast injury in US military overseas contingency operations: a retrospective study. *Annals of Surgery*, 251(6), 1140–1144. <https://doi.org/10.1097/SLA.0b013e3181e01270>
154. Owens, B. D., Kragh, J. F. J., Macaitis, J., Svoboda, S. J., & Wenke, J. C. (2007). Characterization of extremity wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *Journal of Orthopaedic Trauma*, 21(4), 254–257. <https://doi.org/10.1097/BOT.0b013e31802f78fb>

155. Bird, S. M., & Fairweather, C. B. (2007). Military fatality rates (by cause) in Afghanistan and Iraq: a measure of hostilities. *International Journal of Epidemiology*, 36(4), 841–846. <https://doi.org/10.1093/ije/dym103>
156. Leggieri, M. (2011). Computational Modeling of Non-Impact, Blast-Induced Mild Traumatic Brain Injury (mTBI). In *Proceedings from the NATO Symposium: A Survey of Blast Injury Across the Full Landscape of Military Science*. Halifax NS, Canada.
157. Taylor, P. A., & Ford, C. C. (2009). Simulation of blast-induced early-time intracranial wave physics leading to traumatic brain injury. *Journal of Biomechanical Engineering*, 131(6), 61007. <https://doi.org/10.1115/1.3118765>
158. Bolander, R., Mathie, B., Bir, C., Ritzel, D., & VandeVord, P. (2011). Skull flexure as a contributing factor in the mechanism of injury in the rat when exposed to a shock wave. *Annals of Biomedical Engineering*, 39(10), 2550–2559. <https://doi.org/10.1007/s10439-011-0343-0>
159. Goeller, J., Wardlaw, A., Treichler, D., O’Bruba, J., & Weiss, G. (2012). Investigation of cavitation as a possible damage mechanism in blast-induced traumatic brain injury. *Journal of Neurotrauma*, 29(10), 1970–1981. <https://doi.org/10.1089/neu.2011.2224>
160. Panzer, M. B., Myers, B. S., & Bass, C. R. (2013). Mesh considerations for finite element blast modelling in biomechanics. *Computer Methods in Biomechanics and Biomedical Engineering*, 16(6), 612–621. <https://doi.org/10.1080/10255842.2011.629615>
161. Goldstein, L. E., Fisher, A. M., Tagge, C. A., Zhang, X.-L., Velisek, L., Sullivan, J. A., ... McKee, A. C. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Science Translational Medicine*, 4(134), 134ra60. <https://doi.org/10.1126/scitranslmed.3003716>
162. Courtney, M. W., & Courtney, A. C. (2011). Working toward exposure thresholds for blast-induced traumatic brain injury: thoracic and acceleration mechanisms. *NeuroImage*, 54 Suppl 1, S55-61. <https://doi.org/10.1016/j.neuroimage.2010.05.025>
163. Cernak, I., Merkle, A. C., Koliatsos, V. E., Bilik, J. M., Luong, Q. T., Mahota, T. M., ... Ahmed, F. A. (2011). The pathobiology of blast injuries and blast-induced neurotrauma as identified using a new experimental model of injury in mice. *Neurobiology of Disease*, 41(2), 538–551. <https://doi.org/10.1016/j.nbd.2010.10.025>
164. Bhattacharjee, Y. (2008). Neuroscience. Shell shock revisited: solving the puzzle of blast trauma. *Science (New York, N.Y.)*, 319(5862), 406–408. <https://doi.org/10.1126/science.319.5862.406>
165. Chavko, M. T., Adeeb, S., Lankasky, J., Ahlers, S. T., & McCarron, R. M. (2011). Transfer of the Pressure through the Body and its Impact on the Brain. In *Proceedings from the NATO Symposium: A Survey of Blast Injury Across the Full Landscape of Military Science*. Halifax NS, Canada.
166. Mao, H., Unnikrishnan, G., Rakesh, V., & Reifman, J. (2015). Untangling the Effect of Head Acceleration on Brain Responses to Blast Waves. *Journal of Biomechanical Engineering*, 137(12), 124502. <https://doi.org/10.1115/1.4031765>



APPENDIX C:

# DoDD 6025.21E



# Department of Defense DIRECTIVE

NUMBER 6025.21E  
July 5, 2006

USD(AT&L)

SUBJECT: Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries

- References:
- (a) Section 256 of Public Law 109-163, "National Defense Authorization Act for Fiscal Year 2006"<sup>1</sup>
  - (b) DoD Directive 5101.1, "DoD Executive Agent," September 3, 2002
  - (c) DoD Directive 5134.3, "Director of Defense Research and Engineering (DDR&E)," November 3, 2003
  - (d) DoD Directive 5025.1, "DoD Directives System," March 2005
  - (e) through (g), see Enclosure 1

## 1. PURPOSE

This Directive:

1.1. Implements Reference (a) by establishing policy and assigning responsibilities governing coordination and management of medical research efforts and DoD programs related to prevention, mitigation, and treatment of blast injuries.

1.2. Designates the Secretary of the Army, in compliance with Reference (a) and consistent with Reference (b), as the DoD Executive Agent (DoD EA) for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries according to Reference (b).

1.3. Establishes the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. The ASBREM Committee serves to facilitate coordination and prevent unnecessary duplication of effort within DoD biomedical research and development and associated enabling research areas, to include serving as the forum for implementation of subsections (d) and (g) of Reference (a).

---

<sup>1</sup> Federal legislative information is available through the Library of Congress THOMAS site, <http://thomas.loc.gov>. DoDD 6025.21E, July 5, 2006



## 2. APPLICABILITY

This Directive applies to:

2.1. The Office of the Secretary of Defense, the Military Departments, the Chairman of the Joint Chiefs of Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities, and all other organizational entities in the Department of Defense (hereafter collectively referred to as the “DoD Components”).

2.2. Medical and associated enabling research supported by any DoD Component for prevention, mitigation, and treatment of blast injuries.

## 3. DEFINITIONS

As used in this Directive, the following terms are defined as follows:

3.1. Blast Injury. Injury that occurs as the result of the detonation of high explosives, including vehicle-borne and person-borne explosive devices, rocket-propelled grenades, and improvised explosive devices. The blast injury taxonomy is provided at Enclosure 2.

3.2. Research. Any systematic investigation, including research, development, testing, and evaluation (RDT&E), designed to develop or contribute to general knowledge.

## 4. POLICY

It is DoD policy that:

4.1. DoD research related to blast injury prevention, mitigation, and treatment will be coordinated and managed by a DoD EA to meet the requirements, objectives, and standards of the DoD Military Health System as identified by the Under Secretary of Defense for Personnel and Readiness (USD(P&R)) and the unique combat casualty care requirements of the DoD Components.

4.2. Relevant research shall take maximum advantage of the scientific and technical capabilities of industry, academia, DoD Components, and other Federal Agencies.

4.3. The ASBREM Committee will be the venue for joint and cross-Service coordination specified by Reference (a).

4.4. DoD Components will gather and share medical information related to the efficacy of personal protective equipment and of vehicular equipment designed to protect against blast injury.

## 5. RESPONSIBILITIES AND FUNCTIONS

5.1. The Director of Defense Research and Engineering (DDR&E), under the Under Secretary of Defense for Acquisition, Technology and Logistics, according to DoD Directive 5134.3 (Reference (c)), shall:

5.1.1. Plan, program, and execute the functions and reports mandated for the DDR&E by Reference (a).

5.1.2. Have the authority to publish DoD Issuances consistent with Reference (d) for implementation of this Directive.

5.1.3. Establish, as needed, procedures to ensure that new technology developed under this Directive is effectively transitioned and integrated into systems and subsystems and transferred to and firmly under the control of the DoD Components.

5.1.4. Chair the ASBREM Committee to coordinate DoD biomedical research (see Enclosure 3 for additional detail), and employ that entity to facilitate the DoD EA's coordination and oversight of blast-injury research as specified in Reference (a).

5.1.5. Serve as the final approving authority for DoD blast-injury research programs.

5.1.6. Oversee the functions of the DoD EA and conduct/report on related periodic assessments (per Reference (a)).

5.2. The Assistant Secretary of Defense for Health Affairs (ASD(HA)), under the USD(P&R), shall:

5.2.1. Assist the DDR&E, the DoD EA, and the Director, Joint Improvised Explosive Devices Defeat Organization (JIEDDO), with identification of related operational and research needs, assessment of relevant research efforts, and coordination of planning to resolve capability gaps through focused research efforts.

5.2.2. Be the approving authority for Military Health System prevention and treatment standards developed and proposed by the DoD EA.

5.2.3. Appoint appropriate representatives to related coordinating boards or committees established by the DoD EA.

5.2.4. Ensure that the information systems capabilities of the Military Health System support the DoD EA and the functions specified by this Directive.

5.2.5. Serve as Co-chair of the ASBREM Committee. (See Enclosure 3 for additional detail.)

5.3. The Secretary of the Army is hereby designated as the DoD EA for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, consistent with Reference (a), to coordinate and manage relevant DoD research efforts and programs, and in that role shall:

5.3.1. Give full consideration to the Research and Engineering (R&E) needs of the DoD Components and the Director, JIEDDO, addressing those needs/requirements by:

5.3.1.1. Maintaining a DoD technology base for medical research related to blast injuries and based on the DDR&E-approved program for the DoD Components.

5.3.1.2. Performing programming and budgeting actions for all blast-injury research to maintain the R&E programs based on DDR&E-approved priorities of the DoD Components.

5.3.1.3. Programming and budgeting for blast-injury research based on analysis and prioritization of needs of the DoD Components, consistent with paragraph 5.1 of this Directive.

5.3.1.4. Executing the approved DoD blast-injury research program consistent with DoD guidance and availability of annual congressional appropriations.

5.3.2. Provide medical recommendations with regard to blast-injury prevention, mitigation, and treatment standards to be approved by the ASD(HA).

5.3.3. Coordinate DoD blast-injury-research issues with the staffs of the DDR&E, the ASD(HA), and the Director, JIEDDO.

5.3.4. Support the development, maintenance, and usage of a joint database for collection, analysis, and sharing of information gathered or developed by the DoD Components related to the efficacy of theater personal protective equipment (including body armor, helmets, and eyewear) and vehicular equipment designed to protect against blast injury.

5.3.5. Appoint a medical general or flag officer representative to the ASBREM Committee.

5.3.6. Ensure that information is shared as broadly as possible except where limited by law, policy, or security classification and that data assets produced as a result of the assigned responsibilities are visible, accessible, and understandable to the rest of the Department as appropriate and in accordance with Reference (e).

5.4. The Secretaries of the Navy and the Air Force shall:

5.4.1. Forward their respective approved blast-injury medical R&E requirements to the DoD EA for consideration and integration.

5.4.2. Appoint medical general or flag officer representatives to the ASBREM Committee and appoint representatives to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.4.3. Coordinate with other DoD Components on the assignment of Joint Technical Staff Officers to Army medical research entities, research and acquisition organizations, or installations for coordination of research programming and execution needs pertaining to their Component.

5.4.4. Provide an appropriate system for identification, verification, prioritization, and headquarters-level approval of their respective blast-injury R&E requirements before submission to the DoD EA.

5.5. The President of the Uniformed Services University of the Health Sciences (USUHS), under the ASD(HA) and USD(P&R), shall:

5.5.1. Ensure that education relating to blast-injury prevention, mitigation, and treatment is included in the USUHS medical and continuing education curriculum and programs.

5.5.2. Appoint a representative to any coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.6. The Chairman of the Joint Chiefs of Staff shall:

5.6.1. Coordinate input to the DoD EA and ensure integration of the requirements processes of the Joint Capabilities Integration and Development System<sup>2</sup> with the processes employed under this Directive.

5.6.2. Appoint a relevant senior representative to the ASBREM Committee.

5.6.3. Appoint representatives to organizational entities of the ASBREM Committee and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.7. The Commander, US Special Operations Command shall establish procedures and processes for coordination of relevant Defense Major Force Program 11 activities with those planned, programmed, and executed by the DoD EA and shall also:

5.7.1. Forward that command's approved blast-injury R&E requirements for consideration and integration to the DoD EA.

5.7.2. Appoint representatives to organizational entities of the ASBREM Committee, as appropriate, and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.7.3. Coordinate with the command on the assignment of Joint Technical Staff Officers to Army medical research entities, research and acquisition organizations, or installations for coordination of research programming and execution needs.

5.7.4. Provide an appropriate system for identification, verification, and headquarters-level approval of that command's blast-injury R&E requirements before submission to the DoD EA.

5.8. The Director, JIEDDO, consistent with Reference (f), shall:

5.8.1. Support development, maintenance, and usage of a joint database for collection, analysis, and sharing of information gathered or developed by DoD Components related to the efficacy of theater personal protective equipment (e.g., body armor, helmets, and eyewear) and vehicular equipment designed to protect against blast-injury.

5.8.2. Appoint representatives to organizational entities of the ASBREM Committee, as appropriate, and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.8.3. Assist the DoD EA, the DDR&E, and the ASD(HA) with identification of related operational and research needs, assessment of relevant research efforts, and coordination of planning to resolve capability gaps through focused research efforts.

---

<sup>2</sup> 8CJCSI 3170.01E, "Joint Capabilities Integration and Development System," May 11, 2005, is available at [http://dtic.mil/cjcs\\_directives/cjcs/instructions.htm](http://dtic.mil/cjcs_directives/cjcs/instructions.htm).



## 6. AUTHORITY

The DoD EA identified by this Directive is hereby delegated authority to do the following:

6.1. Obtain reports and information, consistent with the policies and criteria of DoD Directive 8910.1 (Reference (g)), as necessary, to carry out assigned responsibilities and functions.

6.2. Communicate directly with the Heads of the DoD Components, as necessary, to carry out assigned functions, including the transmission of requests for advice and assistance. Communications to the Military Departments shall be transmitted through the Secretaries of the Military Departments, their designees, or as otherwise provided in law or directed by the Secretary of Defense in other DoD issuances. Communications to the Commanders of the Combatant Commands shall normally be transmitted through the Chairman of the Joint Chiefs of Staff.

6.3. Communicate with other Federal Agencies, representatives of the Legislative Branch, members of the public, and representatives of foreign governments, as appropriate, in carrying out assigned responsibilities and functions. Communications with representatives of the Legislative Branch shall be coordinated with the Assistant Secretary of Defense for Legislative Affairs and the Under Secretary of Defense (Comptroller)/Chief Financial Officer, as appropriate, and be consistent with the DoD Legislative Program.

## 7. EFFECTIVE DATE

This Directive is effective immediately.



Gordon England

## E1. ENCLOSURE 1

### REFERENCES, continued

- (e) DoD Directive 8320.2, “Data Sharing in a Net-Centric Department of Defense,” December 2, 2004
- (f) DoD Directive 2000.19E, “Joint Improved Explosive Device Defeat Organization (JIEDDO),” February 14, 2006
- (g) DoD Directive 8910.1, “Management and Control of Information Requirements,” June 11, 1993

## E2. ENCLOSURE 2

### TAXONOMY OF INJURIES FROM EXPLOSIVE DEVICES

- E2.1.1. Primary. Blast overpressure injury resulting in direct tissue damage from the shock wave coupling into the body.
- E2.1.2. Secondary. Injury produced by primary fragments originating from the exploding device (preformed and natural (unformed) casing fragments, and other projectiles deliberately introduced into the device to enhance the fragment threat); and secondary fragments, which are projectiles from the environment (debris, vehicular metal, etc.).
- E2.1.3. Tertiary. Displacement of the body or part of body by the blast overpressure causing acceleration/deceleration to the body or its parts, which may subsequently strike hard objects causing typical blunt injury (translational injury), avulsion (separation) of limbs, stripping of soft tissues, skin speckling with explosive product residue and building structural collapse with crush and blunt injuries, and crush syndrome development.
- E2.1.4. Quaternary. Other “explosive products” effects—heat (radiant and convective), and toxic, toxidromes from fuel, metals, etc.—causing burn and inhalation injury.
- E2.1.5. Quinary. Clinical consequences of “post detonation environmental contaminants” including bacteria (deliberate and commensal, with or without sepsis), radiation (dirty bombs), tissue reactions to fuel, metals, etc.



APPENDIX D:

# SUPPLEMENTAL TABLES

**TABLE D-1: FY16 CDMRP Research Programs with Blast Injury-Related Research Activities**

CDMRP Research Program	Program Focus
<p><b>Defense Medical Research and Development Program (DMRDP)</b></p>	<p>The <b>DMRDP</b> provides execution management support for the six DHP core research program areas. Each of these major research program areas is strategically guided by a committee, called a Joint Program Committee (JPC), which consists of DoD and non-DoD medical and military technical experts. The CDMRP provides program and award management support primarily for basic through translational research (Program Elements 6.1 through 6.3) and also works closely with the JPCs to transition products to advanced development.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Develop and field sensors to characterize the potentially injurious environments Soldiers are exposed to during training</li> <li>• Elucidate the complex relationship between vision and TBI, recovery, and impact quality of life</li> <li>• Development and preclinical testing of novel chemotypes as therapies for wound infection</li> </ul>
<p><b>Epilepsy Research Program (ERP)</b></p>	<p>The <b>ERP</b> funds research to develop an understanding of the magnitude of posttraumatic epilepsy (PTE) within the military and to expand research into the basic mechanisms by which TBI produces epilepsy.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Epidemiological characterization and identification of risk factors for developing PTE following TBI</li> <li>• Identification of markers or mechanisms that address PTE</li> <li>• Development of new models or better characterization of existing models for PTE, including repetitive TBI</li> </ul>
<p><b>Joint Warfighter Medical Research Program (JWMRP)</b></p>	<p>The <b>JWMRP</b> funds mature research projects close to yielding tangible benefits to military medicine. The JWMRP focuses on six program areas: Medical Simulation and Information Sciences, Military Infectious Diseases, MOM, CCC, Radiation Health Effects, and CRM.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Simulation technology and medical training</li> <li>• Prophylactics and novel therapeutics to treat multi-drug resistant organisms in combat wound infections, countermeasures that prevent and mitigate Service Member injury</li> <li>• Development and validation of effective evidenced-based prevention, screening and assessment strategies, as well as treatment and rehabilitation interventions for concussion/ mTBI</li> <li>• Identification and development of medical techniques and materiel (medical devices, drugs, and biologics) for early intervention in life-threatening battle injuries</li> <li>• Neuromusculoskeletal injury (including amputees), sensory systems (including balance, vision, and hearing), acute and chronic pain, and regenerative medicine</li> </ul>

Photo credit (opposite page): SPC Scott Lindblom/US Army



CDMRP Research Program	Program Focus
<p><b>Military Burn Research Program (MBRP)</b></p>	<p>The <b>MBRP</b> funds projects that support a broad research portfolio in the treatment of burns and the trauma associated with burn injuries sustained during combat or combat-related activities.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Investigation of the impact of various fluid resuscitation techniques on clinically relevant outcomes during acute burn resuscitation</li> <li>• Studies on single or multiple organ failure in the burn/trauma patient</li> <li>• Evaluation of factors involved in burn wound healing and optimization of strategies for treatment</li> <li>• Impact of prolonged field care and delayed evacuation on patient outcomes</li> </ul>
<p><b>Orthotics and Prosthetics Outcomes Research Program (OPORP)</b></p>	<p>The <b>OPORP</b> funds research that evaluates the comparative effectiveness of orthotic and prosthetic clinical interventions and/or their associated rehabilitation interventions, using patient-centric outcomes for Service Members and Veterans who have undergone limb impairment or limb amputation.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Determination of optimal timing for prosthetic/orthotic intervention and selection of optimal device</li> <li>• Evaluation of comparative effectiveness of different orthotic devices as well as prevention of secondary adverse consequences from prosthetic/orthotic use</li> <li>• Application of specific rehabilitation interventions to accelerate the time, course, or extent of functional outcomes</li> </ul>
<p><b>Peer Reviewed Medical Research Program (PRMRP)</b></p>	<p>The <b>PRMRP</b> funds research across the entire spectrum of medical research toward improving the health and well-being of Service Members, Veterans, and their Families.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Posttraumatic headache</li> <li>• DNA vaccine technology for postexposure prophylaxis</li> <li>• Neuroprosthetics</li> <li>• Posttraumatic osteoarthritis</li> <li>• Tinnitus</li> </ul>
<p><b>Peer Reviewed Orthopaedic Research Program (PRORP)</b></p>	<p>The <b>PRORP</b> funds research to advance the treatment of and rehabilitation from musculoskeletal injuries sustained in combat. The PRORP seeks to optimize recovery and restoration of function following orthopaedic injuries.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Decreasing secondary health effects of reduced mobility following non-spinal cord traumatic neuromusculoskeletal injury</li> <li>• Comparative evaluation of physical/occupational therapy regimens to achieve optimal rehabilitation</li> <li>• Prevention of surgical site/amputation site neuromas</li> <li>• Development of novel materials and technologies to improve performance of prosthetics and orthotics</li> <li>• Development of osseointegration for upper extremity prostheses</li> <li>• Techniques for healing blast-related segmental bone injuries, in which large pieces of bone are lost</li> </ul>

CDMRP Research Program	Program Focus
<p><b>Psychological Health and TBI Research Program</b></p>	<p>The <b>Psychological Health/TBI Research Program</b> funds research efforts aimed at improving prevention, detection, and treatment of psychological health disorders and TBIs. Research funded by Psychological Health/TBI spans the translation research spectrum from basic research to clinical trials.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Investigations of blast physics for improved understanding of mechanism and for enhanced design of PPE</li> <li>• Comparison of behavioral and neural pathologies in blast-induced and mechanically-induced TBI</li> <li>• Evaluation of rehabilitative therapies for TBI injury, including telerehabilitation and virtual reality</li> <li>• Evaluation of neuroprotective and/or therapeutic compounds to treat TBI</li> <li>• Development of field-ready diagnostic devices for PTSD and TBI</li> </ul>
<p><b>Reconstructive Transplant Research (RTR) Program</b></p>	<p>The <b>RTR Program</b> funds innovative research that will foster new directions for, and address neglected issues in, the field of reconstructive transplantation, specifically for vascularized composite allotransplantation (VCA)-focused research.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Immune system regulation</li> <li>• Improved access to reconstructive transplantation</li> <li>• Reconstructive transplantation rehabilitation</li> <li>• Graft surveillance—clinical monitoring</li> <li>• Psychosocial issues associated with VCA</li> </ul>
<p><b>SCI Research Program (SCIRP)</b></p>	<p>The <b>SCIRP</b> funds collaborative research to advance the treatment and rehabilitation of SCI.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Management of acute SCI care (pre-hospital, en route care, and early hospital management)</li> <li>• Best practices for rehabilitation and adjustment to SCI</li> <li>• Research towards the development of spinal regeneration</li> <li>• Secondary health effects and complications following SCI</li> <li>• Investigation and improvement of functional deficits</li> </ul>
<p><b>Vision Research Program (VRP)</b></p>	<p>The <b>VRP</b> funds research efforts to improve and transform the care of military personnel affected by diseases and injuries of the eye. The program focuses on funding innovative, military-relevant research that addresses unmet clinical needs.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> <li>• Mitigation and treatment of traumatic ocular and visual system injuries</li> <li>• Treatment of TBI-induced visual dysfunction, including that caused by direct blast injury</li> <li>• Strategies for the protection, prevention, and rehabilitation of eye injuries</li> <li>• Epidemiological studies of military eye trauma, including TBI-induced visual dysfunction</li> </ul>



ISBN-13: 978-1-947710-10-00-9