FY21

Science & Technology Efforts & Programs

PREVENTION, MITIGATION, AND TREATMENT OF BLAST INJURIES

REPORT TO THE EXECUTIVE AGENT


U.S. NAVY


U.S. MARINE CORPS


U.S. AIR FORCE


U.S. ARMY


U.S. AIR FORCE

DOD Blast Injury Research Coordinating Office ■ U.S. Army Medical Research & Development Command

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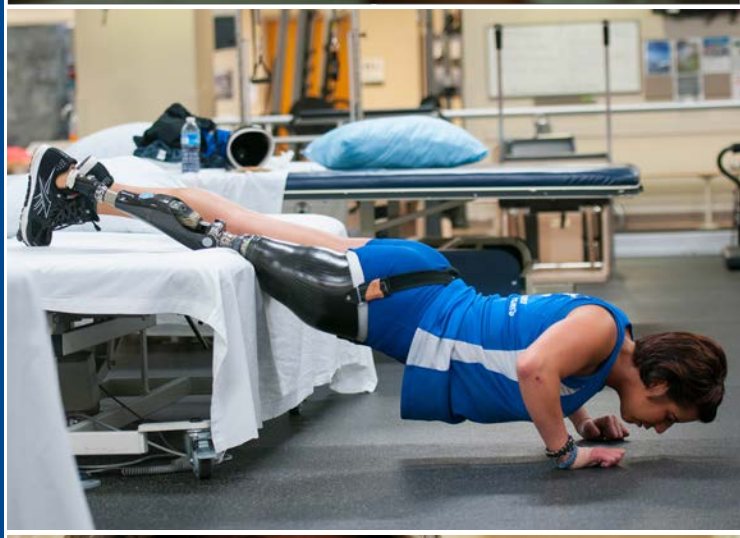

FOREWORD FROM THE DIRECTOR

The DOD Blast Injury Research Coordinating Office (BIRCO) is "meeting the moment" during an extraordinary time in our existence: the end of two decades of combat operations in Afghanistan amid the ongoing COVID-19 pandemic. Each of these events will continue to have lasting impacts on Service members, Veterans, and their Families for the foreseeable future.

In response to a Congressional mandate (Public Law 109-163, Section 256) to improve the coordination of blast injury research, DOD established BIRCO in 2007, at the height of the Iraq and Afghanistan conflicts. Thanks to dedicated researchers, our understanding of blast-related injuries has come a long way, informing everything from the establishment of safety thresholds for human exposure to blasts to improvements in personal protective gear to better outcomes for Service members impacted by a wide range of blast-related injuries. These injuries include, but are not limited to, traumatic brain injury (TBI), hearing loss, burns, and limb loss.

Since BIRCO's inception, the research enterprise has evolved into a more patient-centered partnership, as scientists discovered the importance of studying "what matters most" to people directly impacted by the disease or condition being studied. Research institutions include patients and their families directly in the research process, from the development of the research question to the dissemination of research results, elevating them from study participants to study partners. This paradigm shift will undoubtedly re-shape blast-related injury research as Service members and Veterans impacted by blast injuries integrate as partners in the research process. A great example is the Consumer Advisory Board of the Long-Term Impact of Military-Relevant Brain Injury Consortium Chronic Effects of Neurotrauma Consortium. But there is more work to be done.

Strategic planning across the blast-related injury research community continues to play an important role as researchers work in partnership with front-line medical personnel and Service members impacted by blast injuries to identify and close capability gaps, with the goal of improving injury mitigation.

In FY21, we await the recommendations of the National Academies of Sciences, Engineering, and Medicine (NASEM), from the 2022 edition of the ***Accelerating Progress in Traumatic Brain Injury (TBI) Research and Care*** workshop, commissioned by the DOD and sure to influence the direction of TBI research moving forward. The NASEM committee charged with making the recommendations will be assessing:

- Major barriers and knowledge gaps that are impeding progress in the field
- Opportunities for collaborative action (both intergovernmental and public-private) that could accelerate progress in TBI research and care
- A roadmap for advancing both research and clinical care that would guide the field over the next decade

Lastly, COVID-19 has had an indelible impact on blast-related research in the past year, as Operation Warp Speed caused the diversion of many research laboratories away from their usual efforts toward assisting with the pandemic response. The U.S. Army Medical Research and Development Command (USAMRDC), headquartered at Fort Detrick, Maryland, played a key role in this endeavor, not only in the vaccine development effort but also in assisting medical personnel and studying treatments. BIRCO partner organizations, despite the disruptions, contributed 142 unique research accomplishments to the FY21 EA Report. In these unprecedented times, the dedication of the research community to meet their missions and move the needle on blast-related research is commendable.

Despite COVID-19, BIRCO participated in the 5th International Forum on Blast Injury Countermeasures, held virtually in 2021, focused on the following broad topic areas:

- Blast injury epidemiology and environmental sensing of blast shockwave hazards
- Primary blast injury (due directly to shockwave effects)
- Secondary (penetrating ballistic fragments) and tertiary (acceleration and blunt force blast injury
- Long-term effects, cumulative effects, and chronic symptoms due to blast exposure
- Prevention, mitigation, and treatment of blast injuries
- Diagnostic measures/biomarkers
- Computational modeling and simulation of blast phenomena and blast injury
- Characteristics comparison between blast overpressure-related traumatic brain injury (TBI) and blunt TBI
- New technology and methods for blast injury research and medicine

The goal of the 5th Forum was to engage the international community by bringing together researchers from various disciplines to exchange information on the state of the science and facilitate collaborative opportunities for blast injury research.

The coming year is sure to unveil new challenges and opportunities for the blast-related injury research community as we continue to battle an evolving pandemic and find our way forward. The success of Operation Warp Speed and the heroic scientific effort required to tackle COVID-19 illustrated that a common mission focus can result in life-saving treatments and vaccines developed in record time. Similarly, the mission focus of the blast-related injury research community will continue to yield great benefits in the diagnosis, treatment, and care of our Warfighters. As we look ahead, developing bench-to-bedside strategies focused on "what matters most" to Service members, Veterans, and their Families and aligning our research endeavors with these goals, we can meet the moment successfully.

LTC Jacob D. Johnson
Director, DOD Blast Injury Research Coordinating Office
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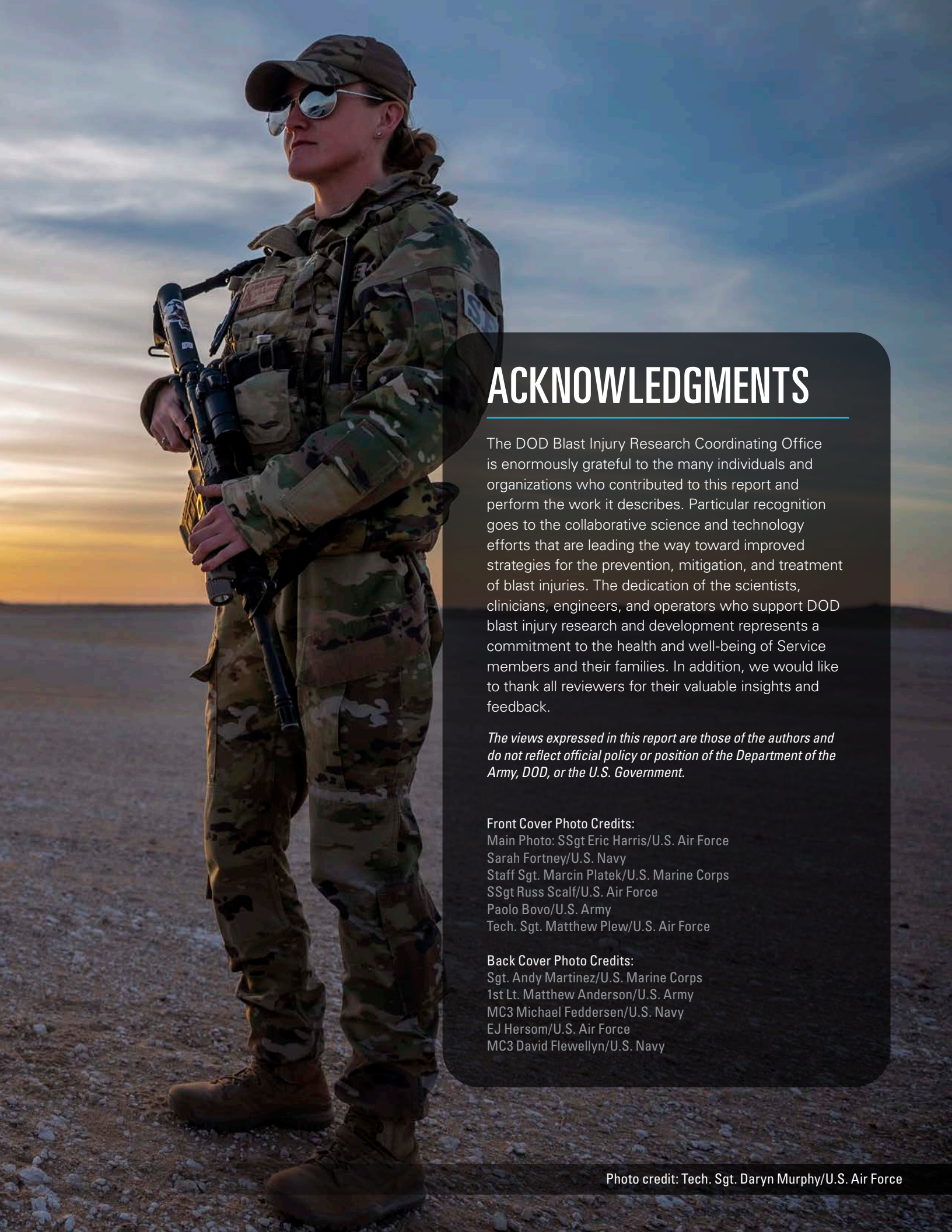

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The views expressed in this report are those of the authors and do not reflect official policy or position of the Department of the Army, DOD, or the U.S. Government.

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EXECUTIVE SUMMARY

The annual report to the DOD Executive Agent (EA) highlights the activities, accomplishments, and plans of the Blast Injury Research Coordinating Office (BIRCO) and the blast injury research community throughout Fiscal Year 2021 (FY21). BIRCO was established In 2007 to help fulfill the DOD EA responsibilities and functions, and support the coordination and management of DOD blast injury research. BIRCO continues its enduring mission to support the DOD EA and advance blast injury research to benefit those who protect and serve the United States.

In 2006, Congress passed critical legislation to address gaps in blast injury research, including Section 256 of Public Law 109-163, the National Defense Authorization Act (NDAA) for FY06, which directed the Office of the Secretary of Defense to designate an EA to coordinate DOD medical research efforts and programs relating to the prevention, mitigation, and treatment of blast injuries. In response, DOD Directive 6025.21E, *Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries*, formally established the DOD Blast Injury Research Program and designated the Secretary of the Army as the DOD EA.

Blast-related injury has become increasingly common in modern warfare, insurgent conflicts, and terrorist attacks worldwide. These injuries encompass the entire injury spectrum (primary to quinary) resulting from blast exposure caused by explosive weapons. In addition to blast exposure in the operational environment, there is interest in the impact of heavy weapons firing on Service members during training activities that could result in similar exposures. Blast injuries can result from the interaction of a blast wave with the body, impact from objects propelled by the blast, or displacement of the body; heat and toxic or radiological substances released from the explosion; or wound infection after injury. Those exposed to blasts often sustain more than one injury, making their

Photo credit: Airman Christopher Storer/U.S. Air Force

treatment highly complex. Even when Service members have mild symptoms from blast injuries (e.g., tinnitus, dizziness, disorientation), they can considerably impact operational readiness and quality of life. The DOD invests significant resources in medical and nonmedical research on the prevention, mitigation, and treatment of blast injuries to address these complexities and optimize the outcomes for those affected by the blast.

Chapter 1 presents an overview of the responsibilities and functions assigned to the EA and other key DOD components for coordinating and managing blast injury research and introduces the framework for characterizing blast injuries, blast injury research, coordination of research and development activities,

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

concluding with a preview of the report. Chapters 2, 3, 4, and 5 outline how BIRCO engages in key initiatives to support research coordination efforts.

- Through the Historical Blast Bio-effects Research Data Recovery Project (2015), BIRCO recovered, digitized, and has made available online 50 years of research data on the biological effects of blast from research conducted at the Albuquerque Blast Test Site on Kirtland Air Force Base, New Mexico from 1951-1998. This DOD Historical Blast Bio-effects Research Data Archive is available for use by DOD and other government-sponsored researchers. In FY21, BIRCO established the Blast Bio-effects Working Group, with members from the U.S. Army Aeromedical Research Laboratory (USAARL) and information management experts from U.S. Army Medical Research and Development Command, to develop a long-term sustainment plan for the Biodynamics Data Resource (USAARL) and the DOD Historical Blast Bio-effects Research Data Archive (BIRCO). More information about these efforts can be found in Chapter 2.

- BIRCO guided the DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats (CMWG). To promote cohesion among modeling and simulation efforts in this space, BIRCO established the working group in 2017 to improve Service member protection and survivability from blast injury. In FY21, the working group drafted a strategic plan to provide actionable, impactful guidance and recommendations for developing a DOD Computational Human Body Modeling Framework. The proposed framework will provide guidelines and best practices for model selection, scenario development, and inter-model communication (e.g., inputs, outputs, and analyses of results). In addition to the strategic plan, the working group developed a prototype Human Body Computational Modeling Registry and a prototype Blast Lethality, Injury, and Impairment Data Sources Registry. Read Chapter 2 for more information about the efforts of this working group and summaries of other BIRCO activities during FY21.

- BIRCO directed the Military Health System (MHS) Blast Injury Prevention Standards Recommendation (BIPSR) Process. The MHS BIPSR Process is the DOD's first unbiased, stakeholder-driven critical assessment methodology for recommending biomedically valid blast injury prevention standards. BIRCO developed the BIPSR Process to support the EA's responsibility of recommending prevention standards. The objectives of the BIPSR Process are to identify existing biomedically evaluated standards for use in the DOD and identify gaps in standards for the research community. The BIPSR Process reviews, supports, and identifies standards that inform and support weapon system health hazard assessments, combat platform occupant survivability assessments, and protection system development and performance testing. In FY21, BIRCO continued to direct the BIPSR Process for auditory blast injuries by completing the evaluation of the Candidate Standards and hosting a meeting with stakeholders to discuss the next steps in the Candidate Standards findings. The next steps are to review the results of these evaluations, develop a draft recommendation, and hold a consensus-building meeting with stakeholders from DOD, academia, and industry. Read more about the MHS BIPSR Process in Chapter 3.

Photo credit: Sgt. Micha Pierce/U.S. Navy

- BIRCO leads a line of inquiry (LOI) on weapon systems for the Section 734 Blast Overpressure Study (BOS). The goal of Section 734 BOS is to address the requirements in Section 734 of the FY18 NDAA, Public Law 115-91, and in subsequent related legislation, improving DOD's understanding of the impact of blast pressure exposure from weapon systems on the Service member's brain and auditory health, and inform policy for risk mitigation, unit readiness, and health care decisions. BIRCO is the Office of Primary Responsibility for one of the five LOIs, LOI 2: Weapon Systems, which aims to develop an improved understanding of the blast exposures resulting from firing or detonating various weapon systems and evaluate existing documentation of the weapon systems in development, testing, training, and modified scenarios. The Blast Overpressure Study (BOS) effort completed a blast overpressure injury threshold review to summarize existing low-level blast overpressure exposure injury thresholds for preventing blast-related brain and auditory injury. The LOI 2 team continued efforts to integrate a BOS Tool into the Range Manager ToolKit—an existing suite of virtual tools that assist Unit Commanders, range safety officials, and others in planning safe range exercises during weapons training. More information about BIRCO's efforts for Section 734 BOS can be found in Chapter 4.

- BIRCO's collaborations with international partners aid in exchanging knowledge and insights on blast injury research to improve our Service members' resilience against blast injury. BIRCO participates in and facilitates several collaborative efforts of global scope and interest with the North Atlantic Treaty Organization (NATO) Science and Technology Organization (STO) Collaboration Support Office (CSO). The CSO supports NATO's defining, conducting, and promoting cooperative research and information exchange. In FY21, BIRCO chaired the HFM-270 Research Task Group (RTG): "Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-related Threats" and HFM-341 (RTG)

ⓘ Throughout this document a reference to section 734 is a reference to NDAA 2018 section 734.

"Validation of Modeling and Simulation Methodologies for Human Lethality, Injury, and Impairment from Blast-Related Threats"; and co-chaired the HFM Exploratory Team (ET)-192 "Blast Exposure Monitoring in Military Training and Operations (BEMMTO)." These NATO-sponsored efforts pool scientific and technical expertise in blast injury from around the world. Chapter 5 has more information about BIRCO's NATO activities.

As part of the EA's mission to facilitate collaboration and promote information sharing, BIRCO welcomes contributions to this report from the blast injury research and development community. The Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) Program Management Office contributed Chapter 6 of this report, which highlights their recent achievements in collecting, integrating, analyzing, and storing operations, intelligence, material, and medical data that would inform solutions to prevent or mitigate injury during the full range of military operations. Finally, in Chapter 7, BIRCO collated 142 submissions of accomplishments from other DOD organizations and partners representing the research, development, testing, and evaluation communities.

Technology played a significant role in the accomplishments submitted to BIRCO in FY21, specifically extending technology-based solutions to Service members in the field to improve diagnosis, accessibility of care, quality of life, and patient outcomes. Notable highlights of the many accomplishments from DOD-funded blast injury research that feature novel uses of technology are below:

- Researchers at the Lightwave Technology Lab at the Missouri University of Science & Technology are developing a Photonics Smart Helmet system for early detection and preclinical diagnosis of traumatic brain injury (TBI) and mild TBI (mTBI). A Photonics Smart Helmet combines a hair-like optical fiber with the shell of a football-style or military-issue combat helmet to create a composite sensor structure. While optical fibers using Fiber-Bragg Gratings conventionally measure strain, bonding the fiber to the surface of a helmet enables accurate measurements of the initial shockwaves and the residual echoes of the impacts as they propagate and reverberate throughout the helmet structures and the Service members' head and neck (page 120).

- A blood-based biomarker laboratory test for TBI, developed by the USAMMDA Warfighter Brain Health (WBH) Project Management Office in partnership with Abbott and Banyan Biomarkers, will greatly enhance the ability of the DOD to objectively assess Service members who have suffered a suspected TBI. The goal of initial implementation will be to assist with managing patients with a suspected TBI, with particular emphasis on implementation in areas where a Service member would otherwise require an evacuation from operational settings to obtain a head CT scan. Laboratory Assay for TBI can potentially reduce unnecessary evacuations, solely for head CT scans, by about 30 percent (page 138).

- Through the Small Business Technology Transfer Program effort at USAARL, researchers will develop an in-ear exposure sensor with integrated noise attenuation and communications capabilities. Presently, military-hardened technologies are not suitable to measure blast exposure due to poor coupling with the head and significant post-processing necessary to correlate sensor motion to head motion. In addition, these technologies must provide communication, along with steady-state and impulse noise attenuation. Through this project, researchers designed, developed, and tested the In-Ear Exposure Sensor for operationally-relevant conditions, producing

a functional prototype capable of measuring head kinematics during blunt impact and blast exposures. In addition to the sensor, researchers also developed a hearable system for impact and blast kinematic measurement. The researchers incorporated accelerometers into both foam and fluidic earplugs and conducted tests, including drop tests, shock tube blasts, linear impacts, shaker table exposures, and sound waves. From these experiments, researchers showed that fluidic earplugs with a single accelerometer have the potential to provide sufficient accuracy for head kinematics while being comfortable and easy to use (page 123).

- A research team led by scientists at the Seattle VA, in collaboration with the Extremity Trauma and Amputation Center of Excellence and the Minneapolis VA, worked to determine whether a brief in-lab trial of prosthetic feet could predict longer-term foot preference. In short, the ability for a patient to "test drive" prosthetic feet would enable them to optimize their prescription faster, thus enabling a more rapid return to their community. Sixty-eight active-duty Service members and Veterans with transtibial amputation trialed three commercial prosthetic feet, and three corresponding emulated feet using a robotic prosthetic foot emulator, which can quickly switch candidate feet, primarily via a software interface (page 184).

- To increase accessibility and meet the clinical demand for mobile vestibular rehabilitation tools, the Naval Health Research Center and the National Intrepid Center of Excellence worked collaboratively with a team of therapists to develop a host of software applications that can be utilized in augmented reality head-mounted display devices, as well as the Computer Assisted Rehabilitation Environment (CAREN), a large-scale virtual reality-based system. These applications include a battery of vestibular tasks (i.e., balance, gaze stability, visual scanning, etc.) with settings that can be individualized to meet specific patient needs and achieve functional goals (page 203).

In the coming year (FY22), BIRCO plans to advance several key initiatives and engagements in blast injury research, including the Sec. 734 BOS program, Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats, and international collaborative activities. In support of Sec 734 BOS, LOI 2 will continue to collect, collate, summarize, and analyze information and findings to identify knowledge gaps and policy deficiencies, with the goal of developing strategies and recommendations for weapons systems. BIRCO will also establish the LOI 2 BOP Tool Module Sub-Working Group to continue to inform refinement, validation, testing, requirements development, and integration of the BOP Tool module. Looking ahead to the conclusion of the Sec 734 BOS effort in FY23, LOI 2 will initiate the development of a technical report that summarizes the findings of LOI 2 activities. In May 2022, BIRCO will organize the 6th International Forum on Blast Injury Countermeasures, where attendees will share experimental laboratory and field study data to increase understanding of the mechanism of blast injury and strategies for prevention, mitigation, and treatment of blast injury. In June 2022, BIRCO will host the NATO HFM-341 (RTG) Kickoff Meeting in Paris, France, where the technical team will present guidelines for the upcoming three years of work, review the Technical Activity Proposal, and establish a program of work. In August 2022, BIRCO will sponsor and organize the 10th International State of the Science Meeting, where multidisciplinary experts from government, academia, and industry will convene for a panel presentation on the state-of-the-science of multiscale computational modeling of the human body's immediate response to blast-related trauma, and engage working groups to provide key recommendations toward a unified computational body model.

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CHAPTER 1:
INTRODUCTION

Blast injuries are complex physical traumas resulting from explosions experienced in combat and non-combat scenarios, including heavy weapons fired in training or in theater. Weapons with a blast component were responsible for the deaths of 82 percent of Service members killed in action (KIA) and for the injuries of 86 percent wounded in action (WIA) in Iraq and Afghanistan between December 2001 and September 2017. During this time, for each KIA there were over eight WIA, and of those wounded, five percent suffered traumatic extremity loss. Those exposed to blast often sustain more than one injury, making their treatment highly complex. In addition, preliminary evidence suggests that repeated, low-level blast exposure due to occupational training, such as breaching or heavy munitions firing, may cause transient physical or psychological changes that adversely affect Service members' performance. Together, these data underscore the need for the DOD's enduring commitment to research and the development of strategies to prevent, mitigate, and treat blast injuries sustained in combat or training.

Civilians are also affected by explosions from both acts of terror and industrial accidents. Of the nearly 200,000 unique events related to terrorism occurring worldwide since 1970, bombings were the most common event affecting both military and civilian populations (Tovar, Bell, & Neal, 2020). On August 26, 2021, at least 182 people, including 13 Service members and 169 civilians, were killed in a suicide bomb attack during an evacuation operation at Hamid Karzai International Airport in Kabul, Afghanistan, marking the first instance of American military casualties in Afghanistan since February 2020. In July 2021, a series of rocket and drone attacks on U.S. diplomats and troops in Iraq and Syria wounded two Service members stationed at Ain al-Asad Air Base (Iraq) and resulted in later TBI diagnoses for dozens more.

Photo credit: Sgt. Sarah Sangster/U.S. Army

Recent history provides additional examples of infamous blasts that caused significant casualties. On August 4, 2020, a massive chemical explosion in Beirut killed over 200 people and wounded approximately 5,000. Several bombings killed more than 250 people and injured more than 400 across Sri Lanka on Easter Sunday in 2019. An explosive was detonated during the morning rush on September 17, 2017, at the Parsons Green station of the London Underground, injuring more than 30 people. On the evening of May 22, 2017, a suicide bomber detonated explosives as teenage fans were leaving a concert at the Manchester Arena in the United Kingdom; the attack killed 23 people and injured 800 others. On April 15, 2013, three people were killed and 264 were wounded when homemade pressure-cooker explosives were detonated during the Boston Marathon.

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

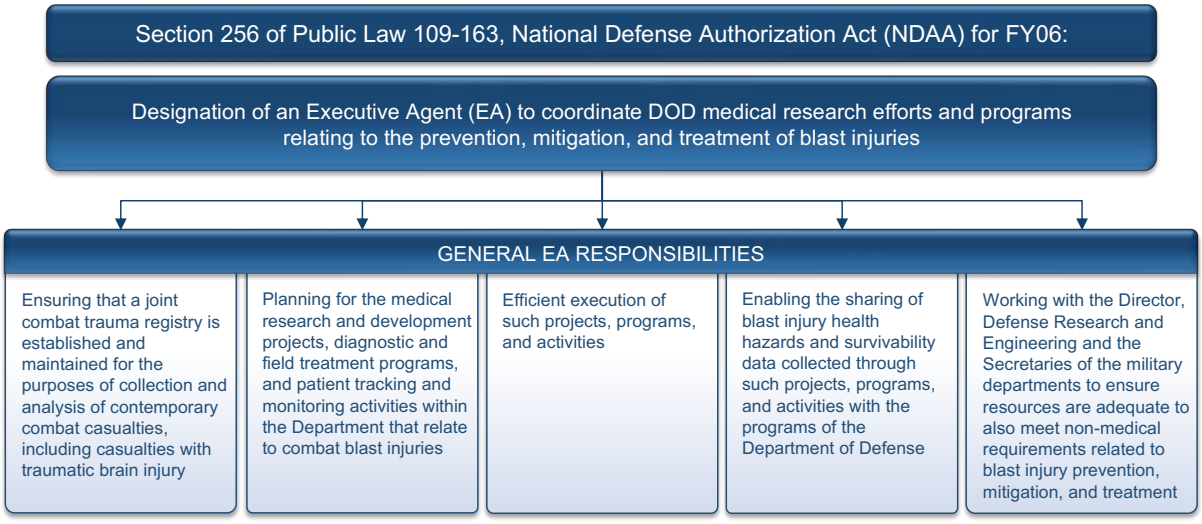
The devastating, often long-term, consequences of blast exposure emphasize the importance of coordinating research investments for the prevention, treatment, and rehabilitation of blast injuries. In 2006, Congress passed legislation to address critical gaps associated with blast injury research (Figure 1-1). Through the National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2006, Public Law 109-163, Section 256, Congress directed the Office of the Secretary of Defense to designate an Executive Agent (EA) to coordinate DOD medical research efforts and programs relating to the prevention, mitigation, and treatment of blast injuries (Figure 1-2). In response, the DOD developed the DOD Directive (DODD) 6025.21E, Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, to establish the DOD Blast Injury Research Program on July 5, 2006. (see Appendix C: DODD 6025.21E).

DODD 6025.21E designates the Secretary of the Army (SECARMY) as the DOD EA. SECARMY delegated authority and assigned responsibility to execute EA responsibilities directly to the Commander, U.S. Army Futures Command.

The DOD Blast Injury Research Coordinating Office (BIRCO), established and chartered at U.S. Army Medical Research and Development Command (USAMRDC) in 2007, supports the EA by coordinating DOD-sponsored biomedical research programs aimed at preventing, mitigating, and treating blast-related injuries; identifies knowledge gaps and shapes research programs accordingly; promotes information sharing among the operational, intelligence, medical, and materiel development communities; and facilitates collaborative research among DOD laboratories and the laboratories of other federal agencies, academics, and industry (Figure 1-3). This allows blast injury researchers to leverage resources and take full advantage of the body of knowledge that resides both within and outside the DOD to accelerate the delivery of blast injury prevention and treatment strategies to Service members.

FIGURE 1-2: Assignment of EA Authority

FIGURE 1-1: Section 256 of Public Law 109-163



BIRCO chooses its initiatives and engagements to support these lines of effort and aid researchers across the DOD, other federal agencies, academia, industry, and international partners in solving complex challenges related to blast injury. In FY21, BIRCO realigned with Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC), which functioned as a separate, enduring program of record since March 2013. The JTAPIC Program was established in 2006 to assist the EA in fulfilling portions of its responsibilities under DODD 6025.21E, specifically support of the development, maintenance, and usage of a joint database for blast research-related information. The JTAPIC 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-related injuries. The JTAPIC Program leverages the medical, intelligence, operational, and materiel expertise of its partnerships to support operational planning and the development of strategies to prevent or mitigate injuries during combat.

Read more about the JTAPIC Program in Chapter 6.

FIGURE 1-3: Breadth of BIRCO's Coordinating Responsibilities

Joint Improvised Threat Defeat Organization (JIDO); Joint Intermediate Force Capabilities Office (JIFCO); Technical Support Working Group (TSWG); North Atlantic Treaty Organization (NATO); Uniformed Services University of the Health Sciences (USU); United States Special Operations Command (USSOCOM); Defense Advanced Research Projects Agency (DARPA).

Responsibilities and Functions

DODD 6025.21E assigns key DOD components specific responsibilities to coordinate and manage the medical research efforts and DOD programs related to the prevention, mitigation, and treatment of blast injuries. For a more detailed description, please see Appendix C: DODD 6025.21E.

- **The Under Secretary of Defense for Research and Engineering (USD(R&E))** oversees the functions of the DOD EA; establishes procedures to ensure new technology developed under the DODD is effectively transitioned, integrated into existing systems, and transferred to DOD components; chairs the Armed Services Biomedical Research, Evaluation, and Management (ASBREM) Communities of Interest (CoI) (now called the Biomedical CoI); and serves the final approving authority for DOD blast injury research programs.

  The purpose of the Biomedical CoI is to sustain and improve the program's responsiveness to medical readiness and warfighting needs; eliminate unwarranted duplication of effort within the program; promote program efficiency, stability, and productivity by optimizing infrastructure, capabilities, coordination, and information exchange among the Services and defense agencies; and provide a forum and mechanism to address program and management issues and organizational roles among the same. The Biomedical CoI is composed of seven sub-groups. Each technical sub-group focuses on specific topics within biomedicine:
  a. Biomedical Informatics/Health Information Systems & Technology (BI/HIST)
  b. Military Infectious Diseases (MID)
  c. Military Operational Medicine (MOM)
  d. Combat Casualty Care (CCC)
  e. Medical Radiological Defense (MRD)
  f. Clinical and Rehabilitative Medicine (CRM)
  g. Medical Chem-Bio Defense (MCBD)

- **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 that MHS information systems capabilities support the EA.

- **In 2021, the SECARMY** delegated authority for the DOD EA for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries to the Commander, U.S. Army Futures Command, who, as the delegated EA, coordinates and manages DOD blast injury research efforts and programs through the following tasks:
  a. Maintaining a DOD technology base for medical research related to blast injuries
  b. Performing programming and budgeting actions for all blast injury research based on analysis and prioritization of DOD component needs
  c. Providing medical recommendations on MHS blast injury prevention, mitigation, and treatment standards
  d. Supporting the development, maintenance, and usage of a joint database for the 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
  e. 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 through the EA.

Photo credit: Lt. Col. Ross Franquemont/U.S. Air Force

- **The President of the Uniformed Services University of the Health Sciences (USU)** ensures that the USU medical education curriculum and programs include topics relating to blast injury prevention, mitigation, and treatment. The USU 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** coordinates all blast injury efforts and requirements through the EA, appoints a senior member to the Biomedical CoI, and appoints representatives to any other coordination boards or committees related to blast injury research.

- **The Commander, U.S. 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 Biomedical CoI and any other coordination boards or committees related to blast injury research.

- **The Joint Improvised Explosive Devices Defeat Organization (now the Joint Improvised Threat Defeat Organization under the Defense Threat Reduction Agency)** supported the development, maintenance, and use of a joint database, focused on the efficacy of in-theater personal protective equipment (PPE) and vehicular equipment designed to protect against blast injury, by helping to establish the JTAPIC Program at USAMRDC. The JTAPIC Program fulfills the intent of a "joint database" by establishing a process that enables data sharing and analysis across communities. On-going responsibilities include identifying related operational and research needs, coordinating research efforts to resolve capability gaps, and appointing representatives to the Biomedical 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 injuries that can result from exposure to explosive weapons. 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. This taxonomy assigns blast injuries to five categories: primary, secondary, tertiary, quaternary, and quinary (Table 1-1). Blast injuries referred to in this report may include any injury, or multiple injuries, from these five categories.

Blast Injury Research Program Areas

Blast injury research 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, current research efforts must actively pursue new tools and understanding in each of three research areas: injury prevention, acute treatment, and reset (Figure 1-4).

TABLE 1-1: Taxonomy of Injuries from Explosive Devices

Type of Blast Injury		Description
 **PRIMARY**	• Blast lung • Ear drum rupture and middle ear damage • Abdominal hemorrhage and perforation • Eye rupture • Non-impact induced mild TBI	Primary blast injuries result from the high pressures created by a blast. These high pressures, known as blast overpressure, can crush the body and cause internal injuries. Primary blast injuries are the only injury classification that is unique to blast.
 **SECONDARY**	• Penetrating ballistic (fragmentation or blunt injuries) • Eye penetration • Mild to severe brain injury	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.
 **TERTIARY**	• Fracture and traumatic amputation • Closed and open brain injury • Blunt injuries • Crush injuries	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.
 **QUATERNARY**	• Burns • Injury or incapacitation from inhaled toxic fire gases	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.
 **QUINARY**	• Illnesses, injuries, or diseases caused by chemical, biological, or radioactive substances	Quinary blast injuries refer to the clinical consequences of post- detonation environmental contaminants, including chemical, biological, and radioactive substances (e.g., dirty bombs).

from DODD 6025.21E

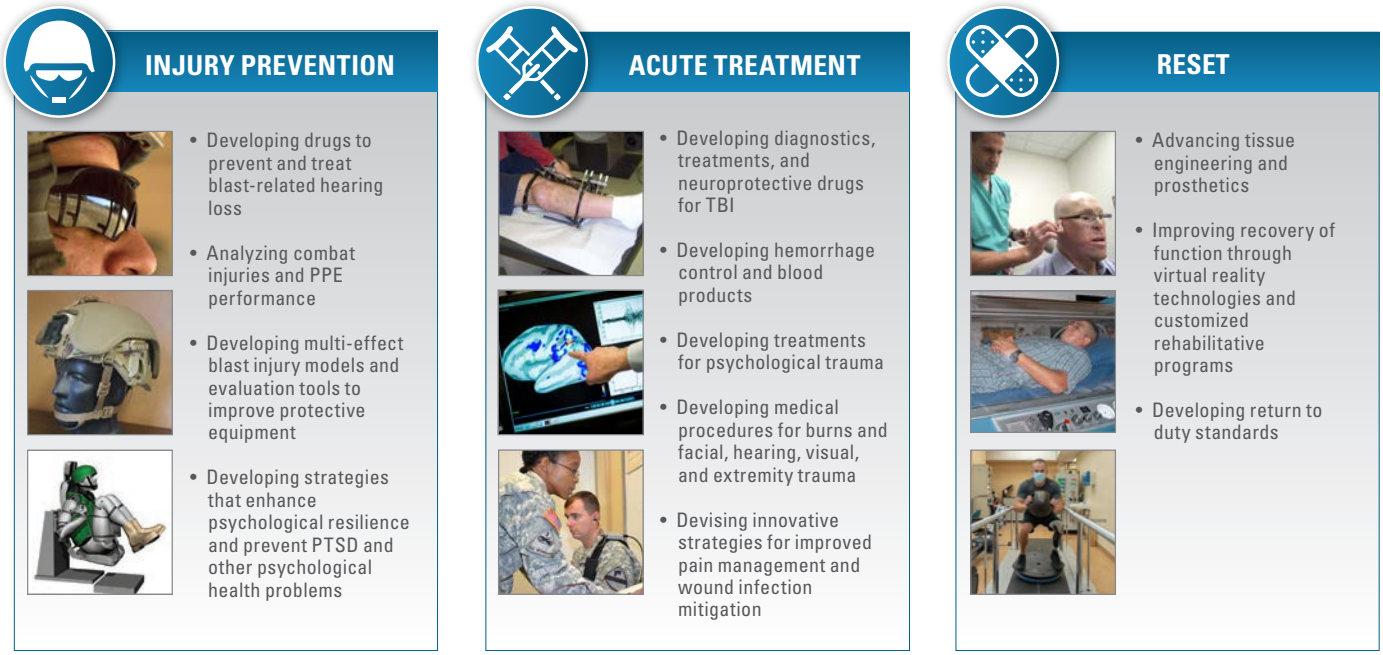


FIGURE 1-4: Blast Injury Research Program Areas

Post-traumatic stress disorder (PTSD); traumatic brain injury (TBI). Photo credits: Column 1—U.S. Marine Corps, U.S. Naval Research Laboratory, U.S. Army; Column 2—U.S. Army Medical Command, U.S. Army Medical Research and Development Command, U.S. Army; Column 3—U.S. Air Force, Defense Advanced Research Projects Agency, Naval Medical Center San Diego.

Injury Prevention

Injury prevention mitigates and reduces the risk of sustaining 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 training to prevent or mitigate injuries.

Acute Treatment

Research and development 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 the development and implementation of new blast injury management strategies, including diagnostic tools, interventions, and clinical guidelines designed to save lives and improve outcomes following hemorrhage, TBI, burns, and damage to extremities and sensory systems, as well as complex polytrauma injury patterns involving blast. This research program area will lead to a greater understanding of the capabilities and limitations of current technologies, as well as new tools and validated methods for blast injury mitigation in the pre-hospital setting.

Reset

Research and development in the area of **reset** aims to mitigate disability by providing a biomedically- based performance assessment capability for return to duty and redeployment following injury; with the goals of rebuilding full performance capabilities in redeployed individuals and restoring function and ability to seriously injured Service members with prosthetic devices. Reset acknowledges a concept that extends beyond rehabilitation to include all activities necessary to return injured Service members to duty or productive civilian lives.

Coordination of Blast Injury Research and Development Activities

The DOD follows a requirements-driven approach to blast injury research and development, with the goals of preventing injuries, treating injuries, and resetting after injury. In pursuit of these goals, the DOD has established numerous research management programs, advisory groups, and stakeholder collaboration activities that address various aspects of blast injury research. Examples of these programs and efforts are highlighted here. Promoting and maintaining effective coordination among these groups is essential to making sustained progress in injury prevention, acute treatment, and reset after injury.

DOD Component Services and Agency Research and Development Programs

The Defense Advanced Research Projects Agency (DARPA) and each of the Services have blast injury research programs primarily funded through the President's Budget. These programs support research within DOD laboratories and clinical centers and through academic and industry partnerships. DOD blast injury research focus areas include injury surveillance, combat casualty care, military operational medicine, and clinical and rehabilitative medicine.

Defense Health Agency Research and Development Directorate

Established in FY14 by the Office of the Assistant Secretary of Defense for Health Affairs (OASD(HA)), the Defense Health Agency Research and Engineering Directorate (DHA R&E) oversees medical research, development, test, and evaluation (RDT&E) programs related to the health care needs of Service members. DHA R&E manages the RDT&E funds of the Defense Health Program. Joint Program Committees (JPCs), which consist of DOD and non-DOD technical experts, make funding recommendations for research and manage the research programs under DHA R&E in diverse military medical program areas, including

Photo credit: Kevin C Mcdevitt/U.S. Army

those that address blast injuries. (See Table 1-2.) These collaborative research programs rely on the expertise and capabilities found across the Services, U.S. Department of Veterans Affairs (VA), U.S. Department of Health and Human Services, academic centers, industry partners, and other scientific and technical communities.

TABLE 1-2: Joint Program Committees

JPC	DHA R&E Program Areas
JPC-2	Military Infectious Diseases
JPC-5	Military Operational Medicine
JPC-6*	Combat Casualty Care Medical Simulation and Information Sciences (formerly JPC-1) Radiation Health Effects (formerly JPC-7)
JPC-8**	Clinical and Rehabilitative Medicine

* During FY21, JPC-1 and JPC-7 were combined with JPC-6.
** During FY20, JPC-8 was dissolved and its research portfolios integrated with JPC-5 and JPC-6.

Congressionally Directed Medical Research Programs

The Congressionally Directed Medical Research Programs (CDMRP) is a global funding organization managing targeted biomedical research programs in cancer research, military medical research, and other disease- and injury-specific research areas. CDMRP represents a unique partnership among Congress, the military, and the American public that invests congressionally directed dollars (not a part of presidential budget request) to fund groundbreaking, high-impact research awards. CDMRP works collaboratively within the DoD, other members of the federal (e.g., NIH and VA) and non-federal medical research community, as well as with consumer advocates, to focus its investment in meritorious research that synergistically targets critical gaps, including several in areas highly relevant to blast injury research. Appendix D: Supplemental Tables lists the CDMRP research programs with recent focus areas relevant to blast injury research.

Centers of Excellence

In response to congressional requirements within the FY08 NDAA, Public Law 110-181, the DOD established several clinical Centers of Excellence (CoE). These centers seek to improve clinical care capabilities using new and updated clinical practice guidelines and policy recommendations; understand injury and outcome trends; and inform research sponsors about the needs and requirements of the clinical community. As a part of their mission, several CoEs address blast injury research, including the Defense and Veterans Center for Integrative Pain Management, DOD–VA Extremity Trauma and Amputation Center of Excellence, National Intrepid Center of Excellence, and those that are now part of DHA R&E: DOD–VA Vision Center of Excellence, Hearing Center of Excellence, Psychological Health Center of Excellence, and TBI Center of Excellence.

Research Forums, Consortia, and Programs Supporting Blast Injury Research

Numerous ongoing collaborative efforts (e.g., working groups, consortia, research programs) are also 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 rehabilitation. Table 1-3 contains examples of collaborative research efforts that involve the DOD and are related to blast injury research.

DOD Component Services and Agency Product Development Programs

The goal of DOD-funded blast injury research is the transition of research outcomes to fielded solutions for Service members. Product development is the process of selecting, maturing, and testing safe, effective, and sustainable medical capabilities to meet military needs. It includes the evaluation of potential solutions to medical capability gaps, guiding medical products through U.S. Food and Drug Administration (FDA) approval or licensing, and supporting the fielding and sustainment of the final product. The U.S. Army Medical Materiel Development Activity (USAMMDA) at USAMRDC is the DOD's medical product development activity. USAMMDA conducts product development through four project management offices: Warfighter Brain Health; Warfighter Expeditionary Medicine and Treatment; Warfighter Health, Performance, and Evacuation; and Warfighter Protection and Acute Care.

Photo credit: Mass Communication Specialist 1st Class Caine Storino/U.S. Navy

Preview of this Report

The following chapters highlight efforts by BIRCO and the blast injury research community to advance the DOD's ability to prevent, mitigate, and treat blast injury.

- Chapter 2 describes BIRCO's strategic approach and key activities during FY21 to facilitate collaboration, identify blast injury research knowledge gaps, disseminate blast injury research information, shape research programs to address knowledge gaps, and promote information sharing and partnerships.

- Chapter 3 describes how BIRCO is advancing the MHS Blast Injury Prevention Standards Recommendations Process.

- Chapter 4 focuses on the NDAA Section 734 Blast Overpressure Study Program's efforts to understand cumulative blast overpressure exposure and its association with long-term effects on brain health.

- Chapter 5 provides an overview of BIRCO's engagement with NATO-led, multi-disciplinary science and technology research panels on blast injury.

- Chapter 6 was contributed by JTAPIC and describes their ongoing programs responsible for collecting, integrating, analyzing, and storing operations, intelligence, materiel, and medical data to inform solutions that prevent or mitigate injury during the full range of military operations.

- Chapter 7 presents the latest accomplishments in blast injury RDT&E supported by the DOD. These accomplishments include scientific advancements, improvements in standards of care, and the development of products to prevent, diagnose, and treat blast injuries.

- Chapter 8 is a discussion of the way forward for BIRCO and the blast injury research community in FY22.

TABLE 1-3: Examples of DOD research forums, consortia, and programs supporting blast injury research

DOD Entity	Blast-Related Efforts
Acute Effects of Neurotrauma Consortium	The **Acute Effects of Neurotrauma Consortium (AENC)** focuses on research into early diagnosis and treatment of TBI. The AENC is an activity of Phelps County Regional Medical Center in partnership with the Leonard Wood Institute, through which university partners study TBI protection, identification, and treatment. (The AENC is separate and distinct from the Long-Term Impact of Military-Relevant Brain Injury Consortium–Chronic Effects of Neurotrauma Consortium [LIMBIC–CENC].)
Armed Forces Institute of Regenerative Medicine	The multi-disciplinary **Armed Forces Institute of Regenerative Medicine** collaborates across numerous agencies to accelerate the development of diagnostic products and therapies for severely wounded Service members in need of reconstructive treatments. The goals of the program are to fund basic through translational regenerative medicine research and to position promising technologies and therapeutic and restorative practices for clinical trials.
Blast Overpressure Studies Working Group	The **Blast Overpressure Studies (BOS) Working Group** is addressing requirements in the FY18 NDAA, Public Law 115-91, Section 734, and FY20 NDAA, Public Law 116-92, Section 742 for a Longitudinal Medical Study on Blast Pressure Exposure of Members of the Armed Forces. The goal of the BOS Working Group is to improve the DOD's understanding of the impact of blast pressure exposure from weapon systems to the Service member's brain and auditory health and better inform policy for risk mitigation, unit readiness, and health care decisions.
Center for Neuroscience and Regenerative Medicine	The **Center for Neuroscience and Regenerative Medicine (CNRM)** is a federal military TBI research program organized as a partnership between USU and the National Institutes of Health (NIH). The CNRM was established by congressional action (Public Law 110-252) as an intramural federal TBI research program focused on the study of blast injury to the brain and post-traumatic stress in Service members. The CNRM consists of more than 20 senior scientific investigators and 50 staff, a robust in-house clinical trials unit, and three clinical support cores. The CNRM has funded 135 research projects and enrolled more than 9,000 research participants, 63 percent of whom are Service members enrolled at nationwide military treatment facilities (MTFs). The CNRM research programs emphasize aspects of high relevance to the military populations, particularly Service members cared for at the Walter Reed National Military Medical Center and those exposed to blast events.
Collaborative Auditory Vestibular Research Network	The **Collaborative Auditory Vestibular Research Network (CAVRN)** is composed of strategically-aligned research laboratories, MTFs, nonprofit and foundation counterparts, industry and academic partners, international bodies, and other government CoEs. CAVRN holds annual meetings to collaborate on areas of hearing and balance issues that Service members and Veterans face as a result of their military service. This growing research network works to advance the community's understanding, spur innovation, encourage interdisciplinary collaboration, and overcome system barriers that may otherwise challenge research.
The Consortium to Alleviate PTSD	The **Consortium to Alleviate PTSD (CAP)** 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. The CAP has completed several of the largest clinical trials of PTSD in DOD history.

DOD Entity	Blast-Related Efforts
DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats	The goal of the **DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats** is to shape, focus, and coordinate efforts to enable a capability for the computational modeling and simulation of human lethality, injury, and impairment resulting from the entire spectrum of blast-related threats. The Working Group includes representatives from DOD organizations and other government agencies.
DOD/USU Brain Tissue Repository	The **DOD/USU Brain Tissue Repository (BTR)** was developed under the auspices of the Center for Neuroscience and Regenerative Medicine (CNRM) of the Uniformed Services University of the Health Sciences (USU) and has now evolved into a separate facility that supports research on military TBI. Housed on the USU campus, the BTR is a brain bank dedicated to collecting brain specimens from deceased Service members, both active duty and retired, following consent for donation and use in research from their legally authorized representative. This facility is the only brain repository exclusively dedicated to exploring the effects of a military career (including blast exposure) on the human brain.
Federal Interagency Traumatic Brain Injury Research Informatics System	The **Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System** was initiated as a collaborative effort supported by the DOD Combat Casualty Care Research Program (CCCRP) and the National Institute of Neurological Disorders and Stroke at the 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. De-identified data from DOD- and NIH-funded clinical TBI studies are required to be uploaded into FITBIR. Benefits include accelerating the testing of new hypotheses, allowing multi-study data aggregation to increase the statistical power, providing existing comparator data, and identifying patterns not easily extracted from a single study.
Interagency Explosives Terrorism Risk Assessment Working Group	The **Interagency Explosives Terrorism Risk Assessment Working Group** was created by the Department of Homeland Security to review progress on the Homeland Explosives Consequence Assessment Tool (HExCAT). The HExCAT is an end-to-end risk assessment tool that includes information from the intelligence community and law enforcement to characterize threat, vulnerability, and interdiction; consequence modeling to calculate the possible range of lethal and sub-lethal injuries; the medical response to an event; and the impact of various security and mitigation strategies.
Linking Investigations in Trauma and Emergency Services	**Linking Investigations in Trauma and Emergency Services (LITES)** is a clinical research network established by the USAMRDC CCCRP in 2016 to sustain and continue the hard-earned advances in military trauma research from more than 15 years of conflict in Iraq and Afghanistan. LITES leverages civilian trauma systems and medical centers to answer trauma and treatment questions to facilitate the narrowing high-priority gaps in the care of severely injured patients. LITES is not a singular research study. Through the task order generation process, independent research studies or analyses can be performed. Each LITES task order is unique, and sites are selected for participation based on the objectives of the specific task order and the site's readiness to participate. Additional information about the current network participants and active task orders can be found here: www.litesnetwork.org
Long-Term Impact of Military-Relevant Brain Injury Consortium–Chronic Effects of Neurotrauma Consortium	**Long-Term Impact of Military-Relevant Brain Injury Consortium – Chronic Effects of Neurotrauma Consortium (CENC) [(LIMBIC–CENC)]** is a joint DOD and VA funding effort addressing the long-term consequences of mild TBI in Service members and Veterans. It continues and expands on the efforts of the original CENC and aligns to initiatives under the National Research Action Plan for Improving Access to Mental Health Services for Veterans, Service members, and Families. The LIMBIC–CENC Coordinating Center is located at Virginia Commonwealth University and executes six studies and three integrated research cores across academic, VA, and DOD research sites. LIMBIC–CENC studies include data and participants with blast exposure history.

DOD Entity	Blast-Related Efforts
Major Extremity Trauma and Rehabilitation Consortium	The **Major Extremity Trauma and Rehabilitation Consortium (METRC)** consists of a network of clinical centers and one coordinating center that works together with the DOD and other sponsoring agencies to conduct multi-center clinical research studies relevant to the treatment and outcomes of traumatic orthopedic injuries. The overall goal of METRC is to produce the evidence needed to establish treatment guidelines for the optimal care of the wounded warrior and ultimately to improve the clinical, functional, and quality of life outcomes of both Service members and civilians who sustain high-energy trauma to the extremities.
The National Collegiate Athletic Association - DOD Grand Alliance: Concussion Assessment, Research, and Education Consortium	The **National Collegiate Athletic Association (NCAA)–DOD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium** is a joint DOD and NCAA research effort dedicated to studying concussion to better understand the development of injury and trajectory of recovery utilizing a multi-site, longitudinal investigation of concussive and repetitive head impacts. Their clinical study also allows for more advanced research projects, such as testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging. In their first award, they focused on the acute effects of concussion; the CARE Consortium enrolled more than 37,000 student-athletes and Service academy Cadets and Midshipmen at 30 sites. In their second award, they focused on the cumulative and persistent intermediate effects of concussion; the Consortium has enrolled more than 53,000 participants. The CARE Consortium will allow scientists to develop evidence-based approaches to understanding the risks, management, and possible treatment strategies for concussion.
Pharmaceutical Intervention for Hearing Loss Working Group	The **Pharmaceutical Intervention for Hearing Loss Working Group** is a working group coordinated by the Hearing Center of Excellence that develops strategies for standardized analysis of potential systemic and local therapies for hearing loss prevention and rescue.
South Texas Research Organizational Network Guiding Studies on Trauma and Resilience	**South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR)** is a DOD-funded, multi-disciplinary, 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. STRONG STAR-established infrastructure supports 18 ongoing studies.
TBI Endpoints Development Initiative	The **TBI Endpoints Development Initiative** is a collaborative, multi-disciplinary team that seeks to advance and validate endpoints that can be used as U.S. FDA-qualified outcomes, such as Clinical Outcome Assessments and blood-based and neuroimaging biomarkers in support of TBI clinical trials.
U.S.–India Project Agreement on Experimental and Computational Studies of Blast and Blunt TBI	The **U.S.–India Project Agreement on Experimental and Computational Studies of Blast and Blunt Trauma Injury** seeks to develop and validate a blast injury animal model for mild TBI using imaging techniques and histological procedures, as well as assessing changes in behavior and cognition; to develop, validate, and cross-validate a computational model for blast and blunt injury; to develop anatomically accurate head/brain models for blast/brain injuries from clinical and experimental data; and to compare the blast and blunt data to develop a scaling ratio.
USU/NIH Traumatic Brain Injury Research Consortium	The **USU/NIH Traumatic Brain Injury Research Consortium (TBIRC)** is an alliance among the various TBI research activities within USU. TBIRC's mission is to ensure research throughout the university is coordinated, streamlined, and visible.

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Photo credit: Lance Cpl. Kimberlyn Adams/U.S. Marine Corps

CHAPTER 2:

DOD BLAST INJURY RESEARCH COORDINATING OFFICE

The DOD Blast Injury Research Coordinating Office (BIRCO) supports the DOD Executive Agent (EA) by coordinating blast injury research inside and outside of the DOD, nationally and internationally, to support the delivery of timely and effective blast injury prevention, mitigation, and treatment solutions for Service members. BIRCO's activities help identify and address knowledge gaps, disseminate information, and minimize duplication of effort. BIRCO promotes collaboration among researchers across the DOD, other federal agencies, academia, industry, and international partners to solve complex challenges related to blast injury. Taking full advantage of the body of knowledge and expertise that resides both within and beyond the DOD, BIRCO advances blast injury research to protect and heal those who serve.

Coordination is a necessary function of DOD blast injury research because of the immensely complex nature of blast injury. Across the DOD, dedicated researchers with deep domain expertise pursue technologically advanced and highly specialized solutions to individual challenges. For example, researchers are advancing tactical measures for rapid medical evacuation, treatment guidance for infection control among blast victims, diagnostic tools for brain function, and therapeutics for severe burns. Coordination enables the DOD to place these efforts within the broad landscape of blast injury research, thus empowering leaders to direct additional resources to mission-critical efforts and to identify trade-offs among them. Coordination also enables researchers to share insights and experiences across disparate lines of effort and to identify complex dependencies. BIRCO's activities are chosen to encourage and support these synergies.

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

Photo credit: Sgt. Sarah Sangster/U.S. Army

MISSION

To assist in fulfilling the DOD Executive Agency responsibilities and functions related to medical research for the prevention, mitigation, and treatment of blast injuries in accordance with DODD 6025.21E by

- Coordinating and managing relevant DOD medical research efforts and programs
- Identifying blast injury knowledge gaps
- Shaping medical research programs to fill identified gaps
- Facilitating collaboration among diverse communities within and outside of the DOD
- Widely disseminating blast injury research information

VISION

To establish and maintain 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.

Advancing Blast Injury Research to Protect and Heal Those Who Serve

DOD Brain Health Research Coordinator

The DOD Brain Health Research Coordinator (the Coordinator), a role within BIRCO, supports the mission of the EA as it relates to neurological and neuropsychological health. The Coordinator is a uniformed officer with experience as a neurology consultant in a combat zone who has held leadership roles at research and clinical organizations within the military. These credentials and background give the Coordinator a unique and nuanced perspective on the DOD's brain health research needs.

The Need for Brain Health Research Coordination

The field of brain health depends on a network of specialists across multiple medical and non medical disciplines:

- Neuroscience
- Neurology
- Neuropathology
- Trauma care
- Primary care
- Medical imaging
- Computational modeling
- Psychology
- Psychiatry
- Rehabilitation
- Drug development
- Nuclear medicine
- Protective equipment development

These diverse efforts present a unique challenge: comprehending the full scope of the state of brain health research and clinical care guidelines across the DOD is a tremendous undertaking. The Coordinator helps the DOD overcome this challenge by facilitating information sharing and partnerships among DOD organizations and between the DOD and external organizations. The Coordinator also helps stakeholders understand the numerous components of the DOD involved in brain health research.

BRAIN HEALTH IS MORE THAN TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is an important component of DOD brain health research, but the field is inclusive of all brain health-related topics important to the Service member, like psychological health and neurodegenerative disease.

In fiscal year 2021 (FY21), the Coordinator engaged in and directed several activities to support the EA's responsibilities to disseminate brain health research and clinical practice information, facilitate collaboration, and promote information sharing among scientists and clinicians within the DOD, other federal agencies, academia, and industry, inside and outside of the U.S.

Board and Advisory Roles

To support the EA's mission to promote information sharing and facilitate collaboration, the Coordinator serves in several research leadership and advisory roles inside and outside the DOD. The Coordinator is the appointed DOD ex officio member of the National Institute of Neurological Disorders and Stroke (NINDS) National Advisory Neurological Disorders and Stroke Council, which recommends support for grant applications, provides recommendations on policies and procedures affecting extramural research, and advises on program planning and concept clearance for NINDS initiatives. The Coordinator is an advisory board member for the University of Michigan Concussion Center, which is working to have better relationships and collaborations with local U.S. Department of Veterans Affairs (VA) medical treatment facilities in its region. As a member of the Scientific Advisory Board for the National Collegiate Athletic Association (NCAA)–DOD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium, the Coordinator reviews updates from NCAA CARE Consortium principal investigators and researchers and participates in discussions on the issues that face the DOD and the NCAA regarding mild TBI/ concussion research, clinical care, and policy.

Photo credit: Lance Cpl. Nathaniel Hamilton/U.S. Marine Corps

In July 2021, the Coordinator was an invited speaker at the virtual Blast Injury Conference, hosted by the Centre for Blast Injury Studies at Imperial College London. His talk opened the "Blast Neurotrauma" session. Researchers from the Walter Reed Army Institute of Research (WRAIR) and Computation Fluid Dynamics Research Corporation (CFDRC) also presented during this session on their work to develop a prototype CoBiare-Blast Tool for understanding and mitigating potentially harmful effects from repeated low-level blast exposure during training with heavy weapons. This project is being conducted with oversight from BIRCO as part of the FY18 National Defense Authorization Act (NDAA), Public Law 115-91, Section 734 Blast Overpressure Study (BOS) effort. The Coordinator also chaired the fifth International Forum on Blast Injury Countermeasures (IFBIC) and provided a talk highlighting the partnership between United States Army Medical Research and Development Command (USAMRDC) and Japanese research experts under the U.S.-Japan Data Exchange Agreement to share information on the state of the science and facilitate collaborative opportunities for blast injury research. (Read more about IFBIC here) Acting in these leadership and advisory roles enables the Coordinator to identify knowledge and research gaps pertinent to brain health and to provide recommendations for research efforts and clinical practices to close these gaps.

Engagement with the Broader Brain Health Community

The Coordinator promotes collaboration among researchers and clinicians from various federal government agencies, academia, and industry through participation in meetings, conferences, and symposia. At these events, the Coordinator interacts with researchers and vendors familiar to the DOD and those seeking routes to

Photo credit: Petty Officer 1st Class Spencer Fling/U.S. Navy

contribute to DOD research efforts. The information and the interactions at these meetings enable the Coordinator to inform research decision-making for the DOD, guide future industry/researcher presentations, and increase the program manager's/executors' knowledge base of TBI research and policy. The Coordinator also ensures that brain health-related recommendations emanating from the BIRCO- International State-of-the-Science Meeting series (SoS) Meetings are shared amongst researchers, clinicians, policy-makers, and senior leaders. This communication facilitates the translation of findings into tangible results that advance the treatment of TBI, blast injury, and neurodegenerative diseases.

In FY21, the Coordinator participated in several impactful brain health-related meetings, conferences, and symposia, including the following:

- Defense Committee on Trauma (DCOT) Committees on Tactical, Surgical, & En Route Combat Casualty Care
- Warfighter Brain Health Capabilities Based Assessment Solutions Development Virtual Working Meeting
- Innovative Research Interchange (IRI) 2020 Virtual Fall Networks Conference
- Defense Health Agency, J7, Education and Training Directorate (DHA-J7), Clinical Communities Speaker Series: Military Health Care: Select Promising Practices (virtual)
- Acute Effects of Neurotrauma Consortium Virtual Conclave
- Armed Services Biomedical Research Evaluation and Management Community of Interest (ASBREM CoI) Annual All Hands meeting
- Arrowhead Publisher's 10th Annual Traumatic Brain Injury Conference (virtual)
- Traumatic Brain Injury Advisory Committee monthly meetings
- Laboratory Assay for TBI Clinical Implementation Operational Assessment working group meetings
- Committee on Accelerating Progress in Traumatic Brain Injury Research and Care, National Academies of Sciences, Engineering, and Medicine (NASEM)
- Peer-Reviewed Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP) Meeting. The Coordinator is a key stakeholder for the FY21 Peer Reviewed TBIPHRP. The TBIPHRP is a Congressional appropriation managed by Congressionally Directed Medical Research Programs (CDMRP) that is focused on research into the prevention, detection, and treatment of traumatic brain injury and improved psychological health for Service members, Veterans, and the public.
- American Academy of Neurology Annual Meeting (virtual)
- Blast Injury Conference, hosted by the Centre for Blast Injury Studies at Imperial College London (virtual)
- 2021 Defense Intrepid Network Research Symposium
- 5th International Forum on Blast Injury Countermeasures (virtual)

BIRCO's Operational Approach

To enable and maintain a ready force that prepares for and responds to new threats within multi-domain operations with agility and speed, it is critical to understand blast effects on Service members better and develop improved strategies to protect against, mitigate, and treat blast injuries. Service members may face new blast-related challenges in the hyperkinetic environment as they overcome enemy area denial and swiftly maneuver to achieve operational objectives. They may need to provide prolonged medical care for blast injuries in resource-constrained settings such as dense urban environments and under austere conditions. They must also be protected from adverse outcomes that may result from occupational exposure to blast events as they train to be ready for the future fight.

BIRCO's Operational Approach (Figure 2-1) supports the blast injury research community in meeting these challenges. BIRCO envisions a fully coordinated DOD blast injury research program that delivers timely and effective injury prevention, mitigation, and treatment strategies to Service members operating in a multi-domain environment today and in the future.

To reach this future state, BIRCO operates through five lines of effort:

1. Identify knowledge gaps
2. Shape research programs to fill knowledge gaps
3. Promote information sharing and partnership
4. Facilitate collaboration within and outside the DOD
5. Disseminate blast injury research information

BIRCO chooses its initiatives and engagements to support these lines of effort and aid researchers across the DOD, other federal agencies, academia, industry, and international partners in solving complex challenges related to blast injury. In FY21, BIRCO realigned with the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) Program, which had been functioning as a separate, enduring program of record since March 2013. The JTAPIC Program was established in 2006 to assist the EA in fulfilling portions of its responsibilities under DODD 6025.21E (Appendix C), in particular, the EA's responsibility to support the development, maintenance, and usage of a joint database for blast research-related information. The JTAPIC Program's mission is to collect, integrate, analyze, and store operations, intelligence, materiel, and

FIGURE 2-1: BIRCO's Operational Approach

National Defense Authorization Act for Fiscal Year 2006 (FY06 NDAA); DOD Directive (DODD); Secretary of Defense (SECDEF); Secretary of the Army (SECARMY); U.S. Army Medical Research and Development Command (USAMRDC).

medical data to inform solutions that will prevent or mitigate injury during the full range of military operations, including blast-related injuries. The JTAPIC Program 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. Read more about the JTAPIC Program in Chapter 6.

Figure 2-2 presents the alignment of key BIRCO initiatives and engagements to these lines of effort. The remainder of this chapter describes BIRCO's efforts for these key initiatives and other activities during FY21.

BIRCO's Key Initiatives in FY21

Blast Overpressure Studies Working Group

BIRCO is a member of the DOD team responding to the National Defense Authorization Act for Fiscal Year 2018 (FY18 NDAA), Public Law 115-91, Section 734, which mandates that the Secretary of Defense conduct a *Longitudinal Medical Study on Blast Pressure Exposure of Members of the Armed Forces*. FY19 NDAA, Public Law 115-232, Sec. 253 and FY20 NDAA, Public Law 116-92, Sec. 717 and Sec. 742 expand on the FY18 mandate. The collective efforts to address these requirements are the Blast Overpressure Studies (BOS); they are also a component of the DOD's overarching Comprehensive Strategy and Action Plan for Warfighter Brain Health. The goal of the BOS is to improve the DOD's understanding of the impact of blast pressure exposure from weapon systems on Service members' brain and auditory health and to better inform policy for risk mitigation, unit readiness, and health care decisions.

The Office of the Assistant Secretary of Defense for Health Affairs leads the BOS effort. The program structure developed to facilitate BOS activities comprises five Lines of Inquiry (LOI), each led by an Office of Primary Responsibility (OPR): Surveillance, Weapon Systems, Exposure Environment, Blast Characterization, and Health & Performance.

BIRCO is the OPR for LOI 2: Weapon Systems. In this role, BIRCO's objectives are to 1) coordinate, collate, and analyze information on blast pressure resulting from high kinetic weapons and events and 2) inform strategies to account for emerging research on the effects of blast pressure exposure on health and performance.

In FY21, the LOI 2 team initiated and coordinated the Blast Overpressure Injury Threshold Review. This endeavor is a cross-LOI effort with the U.S.

FIGURE 2-2: BIRCO's key initiatives and engagements aligned to strategic lines of effort
Military Health System (MHS); Small Business Innovation Research (SBIR); Small Business Technology Transfer (STTR); traumatic brain injury (TBI).

Army Public Health Center (APHC) and TBI Center of Excellence (TBICoE) to summarize information about current low-level blast overpressure exposure injury thresholds for preventing brain, lung, and auditory injury.

Another focus of the LOI 2 team in FY21 was establishing the groundwork to integrate a Blast Overpressure (BOP) Tool module for the Range Manager ToolKit (RMTK)—an existing suite of virtual tools that assist Unit Commanders and range safety officials in promoting safety during weapons training. The RMTK BOP Tool module will provide a new capability and communicate the expected blast overpressure exposure of Service members using, or near, selected weapon systems. This new capability will assist installation range safety officials, Unit Commanders, and others in planning safe range exercises and will inform training decisions (e.g., firing lane distances) and injury risk tolerance decisions (e.g., personal protective equipment, allowable number of rounds). Initial development of the BOP Tool module for the RMTK was performed through a Defense Health Program-funded Small Business Innovation Research (SBIR) project, managed by BIRCO. This effort is also discussed in the Managing SBIRs and Small Business Technology Transfers (STTR) section of this chapter and the Blast Overpressure Studies in Chapter 4.

MHS Blast Injury Prevention Standards Recommendation Process

BIRCO established the Military Health System Blast Injury Prevention Standards Recommendation (MHS BIPSR) Process to fulfill the EA's responsibility to provide medical recommendations for blast injury prevention, mitigation, and treatment standards. The MHS BIPSR Process is the DOD's first unbiased, inclusive, stakeholder-driven process to identify and assess the suitability and applicability of existing candidate standards and to recommend standards that meet DOD stakeholders' needs with a suitable level of validity, rigor, precision, and confidence. The stakeholders established 14 BIPSR Process Blast Injury Types: lower extremity, spine/back, upper extremity, auditory, dermal burns, skull fracture, pelvic/urogenital, moderate to severe TBI, thorax, abdomen, mild TBI, face, neck, ocular. The first three are complete, auditory and dermal burns are in progress, and the remaining will be completed in the coming months. BIPSR Process DOD stakeholders previously participated in an unbiased prioritization process that determined the current rank order of execution for remaining Blast Injury Types.

In FY21, BIRCO continued to direct the BIPSR Processes for auditory blast injuries and dermal burns. For the Auditory BIPSR Process, in FY21 a panel of independent subject matter experts (SMEs) with representatives from the DOD, government, academia, and industry individually completed a structured evaluation of the 14 candidate auditory injury prevention standards. The evaluation factors, such as usability and validity, were previously updated and weighted by the panel to maximize the relevance and impact of the evaluations for auditory blast injury prevention. The next steps in the BIPSR Process are to review and finalize the results of these evaluations, develop recommendations, and host a consensus-building meeting with stakeholders from the DOD, academia, and industry. Impacts from the COVID-19 pandemic delayed the SME Panel timeline; the evaluation review is expected to finish mid-FY22, with the consensus-building meeting planned for late FY22.

For the Dermal Burns BIPSR Process, a call for participation led to the formation of the Dermal Burns Focused Stakeholder Committee with members from throughout the DOD. Several SMEs from industry, academia, and government agencies have been interviewed to ensure the state of the science is captured. Additional SMEs will be interviewed in FY22. Impacts from the COVID-19 pandemic delayed convening the kickoff meeting until FY22.

Details on the BIPSR Process, and the Auditory and

Dermal Burn BIPSR Process evaluations, can be found in Chapter 3, BIPSR.

International Collaborations

Advancements in blast injury prevention and treatment for Service members require close collaboration among researchers, clinicians, engineers, and other stakeholders domestically and internationally. BIRCO participates in several collaborative efforts of global scope and interest, which leverage the best talent and technology that the world offers to protect Service members from blast injury. These activities include leading NATO-sponsored efforts to more precisely direct mitigation strategies for blast injury and participating in broad-ranging collaborations with other nations to pool scientific and technical expertise in blast injury. Through BIRCO's collaborative international engagements, the U.S. shares and gains knowledge and insights on blast injury research with many other nations, improving our Service members' resilience against blast injury.

BIRCO chaired two previous Research Task Groups (RTGs) through the NATO Science and Technology Organization Collaboration Support Office's Human Factors and Medicine (HFM) Panel. The NATO HFM-234 (RTG) was tasked with establishing a framework for a new interdisciplinary research area focusing on the environmental toxicology of blast exposure. To meet this goal, collaborators developed a dictionary of blast injury terms; and guidelines for conducting epidemiological studies, reproducing blast exposures in the laboratory, and using animal models in blast injury research. These products are the first international guidelines for conducting blast injury research and were published as a series of articles in BMJ Military Health.

The NATO Human Factors and Medicine (HFM)-270 Research Task Group (RTG) produced a framework for the development of a comprehensive, threat-to-outcome computational modeling capability that can support an agile and streamlined approach to designing, testing, and fielding blast protection equipment. A final technical report is in preparation comprising an extensive literature review of existing computational models, a thorough list of modeling gaps, a robust repository of information on existing modeling capabilities, and a comprehensive dictionary of modeling and simulation terms. Building on the HFM-270 work, BIRCO chairs a new RTG — Validation of Modeling and Simulation Methodologies for Human Lethality, Injury, and Impairment from Blast-Related Threats — which hosted a virtual pre-kickoff meeting on July 28, 2021. The objective of this HFM-341 (RTG), is to develop standardized methodologies and criteria to validate computational models and the simulation approaches established in the HFM-270 for the entire spectrum of blast-related injuries to mounted and dismounted personnel. The outcome will be an approach and criteria to validate component computational models and simulation techniques.

Previous NATO Activities Related to Blast Injury

- **HFM-090:** Test Methodology for Protection of Vehicle Occupants against Anti-Vehicular Landmine Effects
- **HFM-175:** Medically Unexplained Physical Symptoms in Military Health
- **HFM-193:** mTBI in a Military Operational Setting
- **HFM-207 Symposium:** A Survey of Blast Injury Across the Full Landscape of Military Science
- **HFM-234:** Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards
- **HFM-270:** Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-Related Threats

In addition, BIRCO co-chairs with the U.S. Army Military Operational Medicine Research Program, the newly formed NATO HFM-Exploratory Team-192, Blast Exposure Monitoring in Military Training and Operations. The primary purpose of this exploratory team is to understand Service members' occupational health hazards resulting from repetitive use of weapon systems and explosives during their military career. The secondary purpose is to recommend a need for further exploration of strategies to prevent and mitigate unnecessary exposures and sustain Service members' brain health and performance. Outcomes from this effort will include both documentation of known and unknown relationships among blast exposure, brain health, and performance and also strategies used by NATO members to mitigate unnecessary exposures and brain health degradation. On May 26, 2021, BIRCO participated in the pre-kickoff meeting, the purpose of which was to introduce team members and general team member requirements, as well as discuss and finalize plans for hosting the kickoff meeting in early 2022. Read more about BIRCO's involvement with NATO in Chapter 5.

The second International Forum on Blast Injury Countermeasures (IFBIC) was planned for May 2020 but was postponed until September 2021 due to the coronavirus pandemic. IFBIC started as the Japan-U.S. Technical Information Exchange Forum on Blast Injury, through which BIRCO has been collaborating with the National Defense Medical College (NDMC) of the Japan Self-Defense Forces since 2016. The second IFBIC in 2021 was the fifth meeting of the Japan-U.S. Technical Information Exchange Forum on Blast Injury. BIRCO organized the first IFBIC in 2019 after BIRCO and the NDMC of the Japan Self-Defense Forces agreed to open their ongoing information exchange forum to other nations.

In FY21, the Director of BIRCO served as the general chairman of IFBIC, with the Deputy Director as the program chairman. Both roles are co-chaired with counterparts from the NDMC. This year's diverse program comprised keynote and tutorial lectures, as well as paper sessions focused on primary blast-induced traumatic brain injury, secondary blast injury, auditory system, new therapies, protection, modeling and simulation, new imaging, and sensing and human injury and exposure assessments.

International State-of-the-Science Meeting Series

BIRCO established the annual International State-of-the-Science (SoS) Meeting series in 2009 as a unique and enduring capability that leverages the expertise of outstanding scientists, engineers, and clinicians to identify knowledge gaps and to inform future research needed to close the gaps in the prevention, mitigation, and treatment of blast injury. Foundational components of each meeting include a comprehensive background literature review to inform the meeting, panel discussions, presentations by researchers in the field, and working groups chaired by expert panelists that assess the state of the science and make recommendations regarding policy and strategy guidance and future research directions.

In summer 2022, BIRCO will sponsor the Tenth International SoS Meeting on blast-related injuries, which the RAND Corporation will host. The subject of this meeting is "Toward a Unified Multiscale Computational Model of the Human Body's Immediate Responses to Blast-Related Trauma." This meeting will bring together stakeholders from across the DOD, other federal laboratories, academia, and industry, both domestic and international.

The objectives of this upcoming meeting are to present, summarize, discuss, and make recommendations on the following:

1. Assess the state-of-the-science of unified multi-scale modeling of the human body's responses to blast exposure
    a. Assess the targeted efforts to integrate different models across cell tissue, organ, and whole body.

Photo credit: Senior Airman Julianne Showalter/U.S. Air Force

2. Identify major barriers and knowledge gaps that are impeding progress in the field and opportunities for investment in future research
3. Identify additional opportunities for collaborative action (both intergovernmental and public-private) that could accelerate progress in the understanding of the human body's responses to blast trauma research
4. Provide recommendations to:
    a. Advance pre-clinical and clinical research
    b. Determine key policy gaps
    c. Identify areas to advance product development (prediction, protection, prevention)

The literature review and meeting proceedings for all previous International SoS Meetings, including the knowledge gaps and recommendations from the Expert Panels, are available on the BIRCO website https://blastinjuryresearch.health.mil/index.cfm/sos.

DOD Brain Health Research Coordination

Engagement with and coordination among DOD's brain health research community is part of the scope of BIRCO's role in fulfilling the EA's responsibilities. The DOD Brain Health Research Coordinator (BHRC) at BIRCO works on behalf of the EA to promote, support, and coordinate research to yield solutions that improve Service members' brain health in training, in combat, and at home.

BIRCO contributed to DOD's Comprehensive Strategy and Action Plan for Warfighter Brain Health (CSWBH) effort, including the related Capabilities-Based Assessment meetings to identify requirements and gaps in DOD's ability to monitor, optimize, restore and support Service members' brain health. The CSWBH was directed by the Deputy Secretary of Defense on October 1, 2018, to unify and improve efforts across the DOD related to Service members' brain health and countering TBI. BIRCO's engagement in the CSWBH effort supports the EA's responsibilities to identify knowledge gaps at the intersection of blast injury and brain health and shape research to fill those gaps through doctrine, organization, training, materiel, leadership and education,

personnel, facilities, and policy (DOTMLPF-P) solutions. BIRCO's initiatives described elsewhere in this chapter further support DOD brain health research coordination, including the FY18 NDAA, Public Law 125-91, Sec. 734 BOS effort (more details can be found in Chapter 4), and involvement in DOD research planning and evaluation processes.

Three additional examples demonstrate BIRCO's work in the brain health research community during FY21. In early FY21, BIRCO and USAMRDC leadership participated in a brief to representatives from the House & Senate Appropriations Committees (Defense) on TBI and chronic traumatic encephalopathy research efforts and resourcing. This meeting facilitated a shared understanding of the diverse research efforts underway at USAMRDC to support Service members' brain health. BIRCO leadership also participated in the Armed Services Biomedical Research Evaluation and Management Community of Interest (ASBREM CoI) Annual All Hands meeting. ASBREM ensures appropriate engagement of medical stakeholders and subject matter experts that understand unique issues involved in DOD biomedical research and development (R&D) and the larger federal and private sector biomedical R&D community. DOD Directive 6025.21E (Appendix C) identifies the ASBREM Committee as an entity that facilitates the EA's coordination and oversight of blast injury research. BIRCO participated in the Annual All Hands meeting to ensure that blast-related injury knowledge gaps were considered and addressed where possible by the Joint Technology Coordinating Groups that comprise the CoI.

In the spring 2021, BIRCO leadership attended a four-part meeting series hosted by the Committee on *Accelerating Progress in Traumatic Brain Injury Research and Care* from the NASEM. During this meeting series, participants reviewed civilian and military health burdens of TBI; the landscape of TBI care and research; and gaps and opportunities for improving systems from acute care through rehabilitation and beyond. Discussions during these meetings will be used to inform an upcoming report from the Committee and will address the following: 1) Major barriers and knowledge gaps that are impeding progress in the field; 2) Opportunities for collaborative action (both intergovernmental and public-private) that could accelerate progress in TBI research and care; and 3) A roadmap for advancing both research and clinical care that would guide the field over the next decade.

DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats

BIRCO established the DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats (CMWG) to promote coordination among the many modeling and simulation (M&S) efforts that seek to improve protection and survivability from blast injury. The CMWG includes representatives from 28 DOD organizations and other government agencies including the National Institutes of Health, the National Science Foundation, the National Aeronautics and Space Administration, the Federal Bureau of Investigation, the Federal Aviation Administration, VA, U.S. Department of Homeland Security, and the National Highway Traffic Safety Administration.

The objective of the CMWG is to shape, focus, and coordinate efforts to enable an integrated and comprehensive capability for the computational M&S of human lethality, injury, and impairment resulting from the entire spectrum of blast-related threats and environments, from the initial point of interaction with the blast hazard to return-to-routine.

This new modeling capability will make it possible to rapidly develop and assess the impact of innovative personal and combat platform occupant

protection concepts in a virtual environment, accelerate the development of effective treatment strategies, and predict health outcomes and disabilities. Valid predictive models will reduce the number of expensive and time-consuming dynamic tests by identifying only the specific cases that require additional experimental verification. As Service members encounter novel threats in future combat scenarios, this capability will allow the DOD to quickly and adeptly address those threats. Reductions in resources required for Live Fire Test and Evaluation are also an expected outcome.

As envisioned by the CMWG members, the modeling capability is sufficiently broad in scope to allow computational M&S from the time of exposure to the blast hazard through return-to-routine and is depicted in Figure 2-3. The blue block on the left of the schematic, *Module 1: Until Homeostasis is Reached*, represents and focuses on the Service member's condition from the point of injury until clinical homeostasis is reached. The yellow block, *Module 2: Recovery and/or Further Degeneration*, represents and focuses on the Service member's condition from the point of homeostasis as they undergo rehabilitative treatment until either rehabilitation is no longer needed or is stopped because it is not expected to yield an increase in function.

To achieve an integrated modeling capability, the CMWG envisioned a DOD Computational Human Body Modeling Framework (Framework) that will support model selection for scenario development, scenario execution, and analysis of results. Over the course of several meetings and follow-on discussions, the CMWG is developing a strategic plan to provide actionable, impactful guidance and recommendations for developing the Framework to achieve DOD mission impacts. This includes the development of guidelines and best practices for M&S that foster acceptance and adoption of the modeling capability, and ensure that the modeling capability provides credible and actionable guidance for decision-makers. A manuscript for peer-reviewed publication on the technical challenges associated with the development of the Framework is planned for 2022.

FIGURE 2-3: Scope of modeling capability from blast threat to return-to-routine
The modeling capability is represented by everything within the dotted lines and has two modules: 1) Until Homeostasis is Reached and 2) Recovery and/or Further Degeneration.

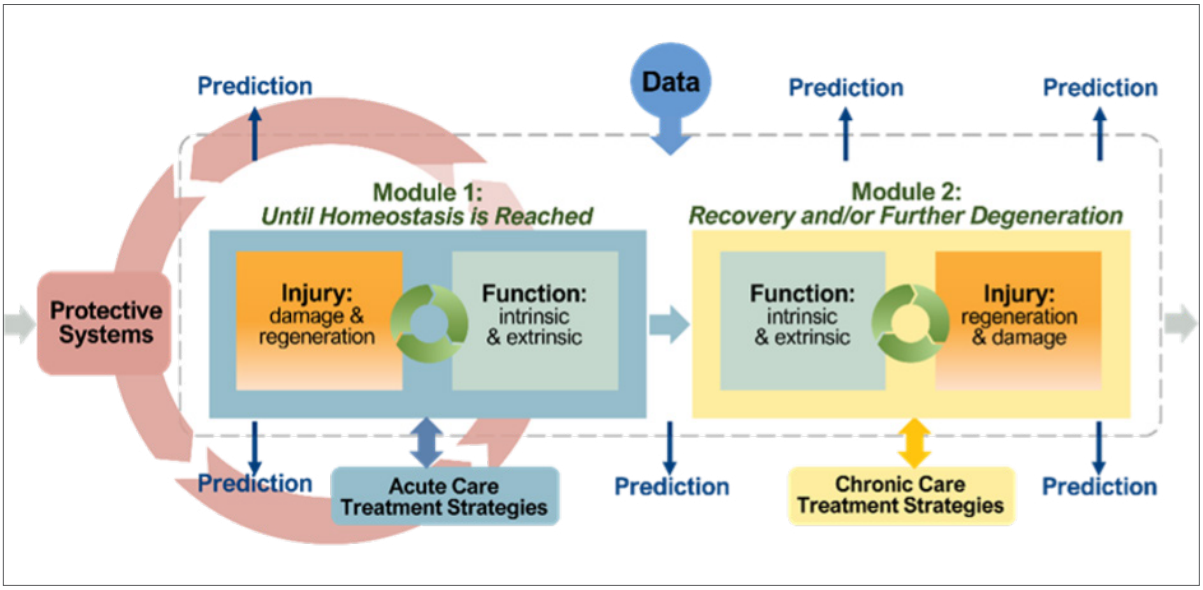


Photo credit: Staff Sgt. David Staten/U.S. Navy

The CMWG strategic plan sets near-, mid-, and long-term strategies to develop, grow, and sustain the Framework for the modeling capability. For the near term, the strategic plan details goals, objectives, actions, assumptions, and performance indicators that will drive the first five years of activity for the Framework. The three central themes of the near-term strategy are to 1) promote a shared vision of the modeling capability among stakeholders, 2) increase stakeholder access to models and data sources, and 3) produce results that influence Service members' lethality and return-to-duty practices.

This CMWG strategic plan aligns with the DOD Digital Engineering Strategy by providing actionable guidance for establishing an enduring modeling capability, registries, and the Framework that allow for an integrated digital approach using authoritative sources of models and data to achieve DOD mission impacts. This includes establishing supporting infrastructure in the Framework and registries to enable collaboration and communication across stakeholders who develop, mature, and utilize the computational modeling capability; formalizing the development, integration, and use of models in the modeling capability; ensuring responsivity to technological innovation; and promoting the use of human body computational M&S to inform, design, and support national defense systems as well as the transformation of the culture and workforce to adopt and support the objectives of the strategic plan.

In addition to the strategic plan, the CMWG developed a prototype Human Body Computational Modeling Registry to act as a centralized resource for users to obtain key metadata and descriptions for computational models and the developers or owners of those models. Information on models developed within the DOD, academia, and industry was captured using a Modeling Questionnaire developed by the CMWG and is included in the Modeling Registry. Model information is organized and searchable

by criteria such as body region, use case, blast taxonomy, validation and verification, required data, and simulation type.

The CMWG also developed a prototype Blast Lethality, Injury, and Impairment Data Sources Registry to house information about data sources that inform human body computational models. As with the Modeling Registry, the CMWG developed a Data Sources Questionnaire to capture pertinent information about the data sources on lethality, injury, and impairment effects from blast-related threats, and related to Service member recovery from those effects. Collected information is organized and searchable within the Data Sources Registry by criteria such as use case, data collection methods, the timeframe of data collection, blast threat, spatial resolution, standardized data format, and information on how to access data.

In FY22, BIRCO plans to finalize the strategic plan, continue to add new information to the Modeling and Data Sources Registries, identify potential steward organizations for the registries in perpetuity, and foster and grow engagement in and commitment to the Framework through established and novel pathways.

The actions of the CMWG have garnered interest from high-level stakeholders outside the DOD regarding the critical role that improved, credible M&S in coordination with data science and analytics for accelerating injury prevention, mitigation, and treatment strategies. In May and September 2020, BIRCO, on behalf of the CMWG, provided an invited briefing on the goals and activities of the CMWG to the Director and members of the Board of Mathematical Sciences and Analytics for the NASEM, and their colleagues from several academic institutions. The CMWG and the National Academies plan to continue engaging to further their mutual goals.

Annual Report to the Executive Agent

BIRCO's annual report to the EA covers research and development efforts and programs focused on the prevention, mitigation, and treatment of blast injuries. Intended to inform senior DOD policy-makers, researchers, and public audiences, the annual report to the EA highlights blast injury research accomplishments across the DOD within that fiscal year that address the full spectrum of blast injuries. These reports are available on the BIRCO website https://blastinjuryresearch.health.mil/index.cfm/annual_reports.

Every annual report features significant achievements from the year submitted by the blast injury research community. This survey of blast injury prevention, treatment, and reset accomplishments broadly showcases research and development advancements to inform the EA and the blast injury research community of the state of the field. Research and development accomplishments from FY21 are presented in Chapter 7 of this report.

In addition to providing accomplishments from the blast injury research community and substantial updates on BIRCO's activities, the annual reports include contributed chapters from stakeholder organizations. For example, the FY20 Report to the EA featured a chapter on the Psychological Health Center of Excellence. This year, the report presents contributions from the Joint Trauma Analysis and Prevention of Injury in Combat on its DOD program with EA responsibility to collect, integrate, analyze, and store operations, intelligence, materiel, and medical data to inform solutions that prevent or mitigate injury during the full range of military operations (Chapter 6).

Managing SBIRs and STTRs

BIRCO actively shapes blast injury research through DOD SBIR and STTR programs. These programs harness the innovative talents and entrepreneurial energies of our Nation's small technology companies to solve research

challenges. BIRCO participates by developing candidate topics for Phase I solicitations in the U.S. Army or DHA SBIR and STTR programs and manages successful proposals funded for these topics. BIRCO managed three SBIR/STTR projects during FY21.

The first project is a follow-on to a previous project that designed and developed a prototype computational modeling framework consisting of improved computational biology tools and whole body and brain injury models for simulations of blast injury and repetitive loading events. Called the CoBi-blast Injury Simulation framework, this anatomically-consistent computational model of how the human body responds to injurious scenarios provides a pathway to better understand blast injuries, interpret experimental data, and develop improved protective armor, diagnostics, and medical treatment procedures. Through coordination with the U.S. Army Training and Doctrine Command and the U.S. Marine Corps, the CoBi-blast Injury Simulation framework and databases are being further consolidated for fast simulation of blast wave interaction with Service members subjected to repeated exposure to blast waves generated by explosive materials and by heavy weapons during military training. The goal of this project is to develop and deliver a professional user-friendly product, CoBi-Blast, as a standalone tool and as a BOP Tool module in the Range Managers Toolkit (RMTK) for use by Service members and instructors involved in weapon training. This new capability could assist installation range management authorities, Service members, unit commanders, and instructors involved in weapon systems training, testing, and combat to make informed decisions on risk assessments.

The second project also focused on the improvement, validation, documentation, and delivery of BOP tools as a module in the RMTK framework. A software interface between the proposed RMTK BOP module and the latest version of RMTK Noise Tool will be designed and adapted for both PC- and tablet-based graphical user interfaces. After successful prototype development, planned next steps include: 1) a prototype interface to the RMTK framework, 2) parametric simulations of blast exposure for selected Tier 1 weapons training, and 3) a prototype database for the collection of experimental data and comparison of results for model-based analytics. The first two projects are also discussed in this chapter's Blast Overpressure Studies Working Group section.

Finally, the third project initiated the final assembly of a biomechanically accurate rat model surrogate that can precisely measure the loading conditions experienced from a blast wave. This capability allows correlation and cross-validation of research outcomes from different studies. Moving forward, the performers aim to validate their primary research findings in the context of existing science, and actionable information can more efficiently be provided to medical researchers, protective equipment developers, and clinical personnel.

Historical Blast Bio-Effects Research Data Archive

Through the Historical Blast Bio-effects Research Data Recovery Project, BIRCO recovered, digitized, and has made available online 50 years of research data on the biological effects of blast from DOD research conducted at Kirtland Air Force Base, New Mexico. This effort allows program managers, researchers, and decision-makers to use existing knowledge to address current and future blast injury problems. Applying lessons learned to current research and product development efforts prevents wasteful duplication of effort and allows the DOD to focus scarce blast injury research resources on other critical knowledge gaps, but not limited to: survivability assessments for military and civilian personnel under numerous hypothetical explosive detonation scenarios, development of treatment strategies for casualties, development of heavy munitions

Photo credit: Steve Thurow/U.S. Air Force

systems that are safe for users, and development of protective equipment to mitigate injury due to explosives.

In early FY21, a working group was organized, with membership comprised of representatives from BIRCO, the USAMRDC Deputy Chief of Staff for Information Management, Military Operational Medicine Research Program, the United States Army Aeromedical Research Laboratory (USAARL), Naval Air Systems Command (NAVAIR), and the Naval Air Warfare Center Aircraft Division. In February 2021, a kickoff meeting was held to orient working group members with BIRCO's Historical Blast Bio-effects Research Data Archive and USAARL's Biodynamics Data Resource. USAARL's database features the most extensive set of biofidelic and injury data about accelerative events, injuries, and fatalities with military relevance; it is a living data resource that will continue to incorporate additional datasets. BIRCO is currently collaborating with USAARL to develop a long-term sustainment plan for both the Biodynamics Data Resource and the DOD Historical Blast Bio-effects Research Data Archive to provide researchers from the DOD, other government agencies, and academia with irreplaceable historical data. In FY22, BIRCO will work to implement a sustainment plan that ensures that both databases are maintained for researchers who wish to contribute to and use the data to further blast research, facilitate data harmonization, and maximize these repositories' impacts on future research discoveries.

The DOD Historical Blast Bio-effects Research Data Archive is available for use by DOD and other government-sponsored researchers and can be accessed through the website https://blastinjuryresearch.health.mil/index.cfm/about_us/initiatives/historical_blast_data_recovery.

Involvement in DOD Research Planning and Evaluation Processes

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

BIRCO's continued engagement with the Joint Program Committees (JPC) and other organizations that manage research portfolios ensures that high-priority blast injury research issues are addressed in future medical research investments. In FY21, BIRCO brought perspectives gained from its research collaboration function to In-Progress Reviews and Review & Analysis meetings for JPC-2/Military Infectious Diseases Research Program, JPC-5/Military Operational Medicine Research Program, JPC-6/Combat Casualty Care Research Program, and CDMRP. These meetings provided a high-level summary of the key areas of each program's medical research investment and highlighted the importance of 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.

Conclusion

Blast injuries include the entire spectrum of injuries that can result from exposure to an explosion. They are highly complex, involving multiple types of injuries and multiple body systems at once. Only a coordinated research effort involving DOD, other federal agencies, academia, industry, and international partners can solve our toughest blast injury research challenges.

Established and chartered in 2007 to support the DOD Executive Agent for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, BIRCO has structured an operational approach to move DOD toward a fully coordinated blast injury research program that delivers timely and effective injury prevention, mitigation, and treatment strategies to our Service members operating in a multi-domain environment today and in the future. Figure 2-4 summarizes recent accomplishments that have resulted from BIRCO's initiatives and engagements as presented throughout this chapter. See Chapter 8 for a preview of BIRCO's activities in FY22 and beyond.

FIGURE 2-4: A summary of recent accomplishments from some of BIRCO's initiatives discussed in this chapter

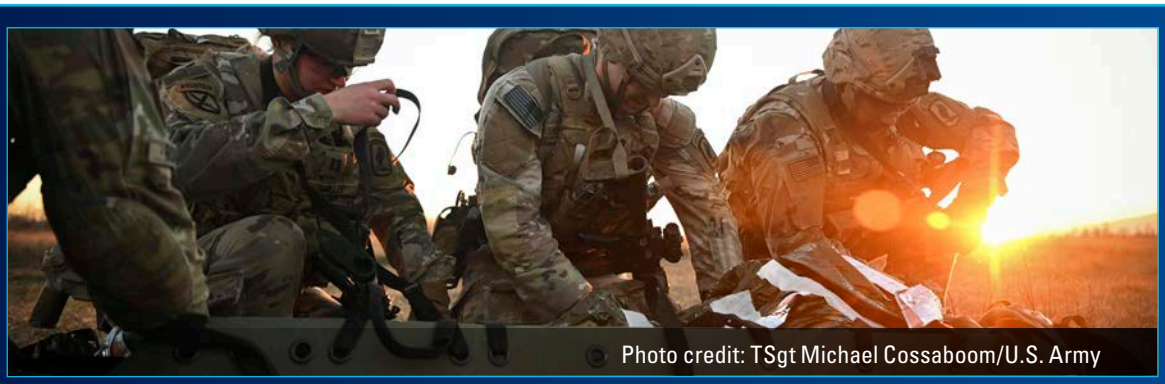


Photo credit: TSgt Michael Cossaboom/U.S. Army

Recent Accomplishments from BIRCO Initiatives

- Established a strategic plan for a computational human body modeling capability
- Initiated a rigorous independent process to evaluate candidate auditory blast injury prevention standards for DOD suitability and use
- Developed the concept of operations and defined interoperability services for the modeling capability for the CMWG
- Initiated the refinement, validation, and development of an integration plan for a new BOP Tool module for the RMTK

Photo credit: Lance Cpl. Ujian /U.S. Marine Corps

CHAPTER 3:

MHS BLAST INJURY PREVENTION STANDARDS RECOMMENDATION PROCESS

The DODD 6025.21E assigns to the DOD Executive Agent (EA) for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries the responsibility to "provide medical recommendations with regard to blast injury prevention, mitigation, and treatment standards to be approved by the Assistant Secretary of Defense for Health Affairs (ASD(HA))." The term "Military Health System (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 Research, Development, Test, and Evaluation (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 3-1).

Designed to address the above requirement, the MHS Blast Injury Prevention Standards Recommendation (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 BIPSR Process also 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.

FIGURE 3-1: Blast Injury Prevention Standards Framework

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

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

Core elements of the BIPSR Process include:

- **BIPSR Process Stakeholders Committee:** A committee that 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 Committee with expertise related to a particular Blast Injury Type. They review existing capabilities which are identified through a literature survey using relevant keywords and captured in a report, identify subject matter experts (SME), identify existing candidate standards, define intended uses and functionalities, 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 (IV&V).
- **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, gain context and scope for the evaluation, and facilitate 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: identify existing capabilities and standards pertinent to the injury under evaluation and compile a list of appropriate experts who may serve on the SME Panel that performs 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 and functionalities defined by the Focused Stakeholder Committee.

The list of candidate standards is narrowed based on an evaluation against a set of defined criteria. The information generated through the evaluation process serves as the basis for a meeting that provides a forum for the Focused Stakeholder Committee to build consensus, share information, and discuss the applicability of a candidate standard to the DOD's intended use and functionalities — 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 test

process focused on Focused 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 SME Panel and BIPSR Process support team conduct final evaluations, develop standards recommendations for discussion with the stakeholders and community at the Consensus Building Meeting, and prepare process improvement recommendations. Collaboration opportunities are integrated across the BIPSR Process. As depicted in Figure 3-2, the BIPSR Process consists of six fundamental subprocesses supporting the overarching seventh.

Each phase in the BIPSR Process is designed to leverage the information from the previous phases, which builds layers of information about the viability of the candidate standards. As a result, the later subprocesses (V and VI) do not necessarily occur in sequence but are iterated as necessary to produce sufficient information to support the recommendations. Table 3-1 contains a high-level description of various activities that take place in the subprocesses that make up the BIPSR Process.

The timeline associated with the 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 Blast Injury Types.

The identification and prioritization of the injury mechanisms fall outside the scope of the BIPSR Process and are the responsibility of BIRCO 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 science and technology communities.

BIRCO developed the BIPSR Process via a series of BIPSR Process stakeholders meetings and obtained Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee approval.

FIGURE 3-2: BIPSR Process Pillars

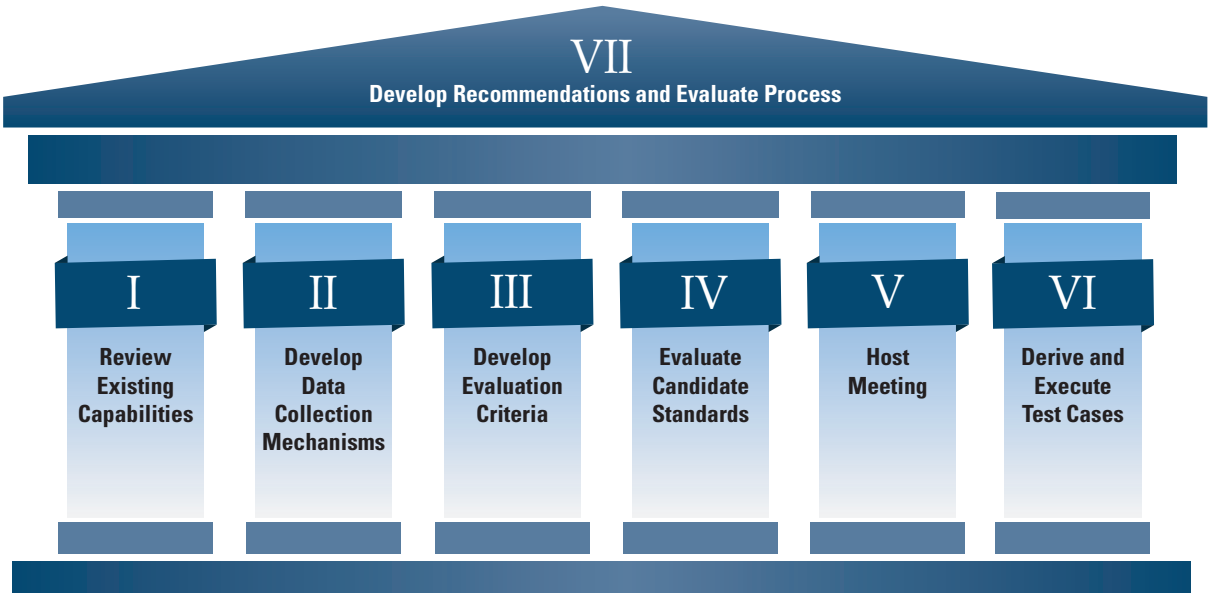


TABLE 3-1: BIPSR Process Pillar Activities

No.	Pillar	Activities
I	Review Existing Capabilities	• Engage stakeholders and identify relevant standards for the injury criteria through a systematic literature survey • Establish a broad-based, independent review panel • Poll the community by issuing a Request for Information (RFI)
II	Develop Data Collection Mechanisms	• Develop standardized evaluation and information templates • Conduct frequent panel meetings to establish review criteria
III	Develop Evaluation Criteria	• Define scenarios and evaluation metrics • Hold a Consensus-Building Meeting
IV	Evaluate Candidate Standards	• Conduct an interactive set of evaluations with the SME Panel and developers
V	Host Meeting	• Hold a Consensus-Building Meeting for stakeholders to share information
VI	Derive and Execute Test Cases	• Involve users and stakeholders in the development of scenario-based test cases and execute the tests for the identified candidate standards (where applicable)
VII	Develop Recommendations and Evaluate Process	• Produce a report that recommends standards for consideration as the basis for MHS Blast Injury Prevention Standards • Recommend improvements to the BIPSR Process

The Johns Hopkins University Applied Physics Laboratory (JHU-APL), a University-Affiliated Research Center (UARC) and DOD trusted agent, supported BIRCO through the piloting of the BIPSR Process with an evaluation and analysis of Toxic Gas Inhalation as an exemplar. Currently, the MITRE Corporation, a DOD trusted agent that operates a federally funded research and development center, supports BIRCO in the execution of the BIPSR Process by working closely with BIPSR Process stakeholders and SMEs in the blast community.

BIPSR Process Improvements

To expedite the timeline required for the evaluation of MHS BIPSR Process Blast Injury Type, BIRCO developed the BIPSR Process simulation model using the business process modeling notation standard. This standard modeling methodology represents the BIPSR Process activities and facilitates quantitative and qualitative analysis via simulation.

As BIPSR Process milestones are reached with each Blast Injury Type under evaluation and stakeholders offer feedback, modifications, and improvements to the BIPSR Process are continually considered and evaluated for implementation.

In addition, the development and implementation of a web-based collaboration environment known as interactive BIPSR (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.

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

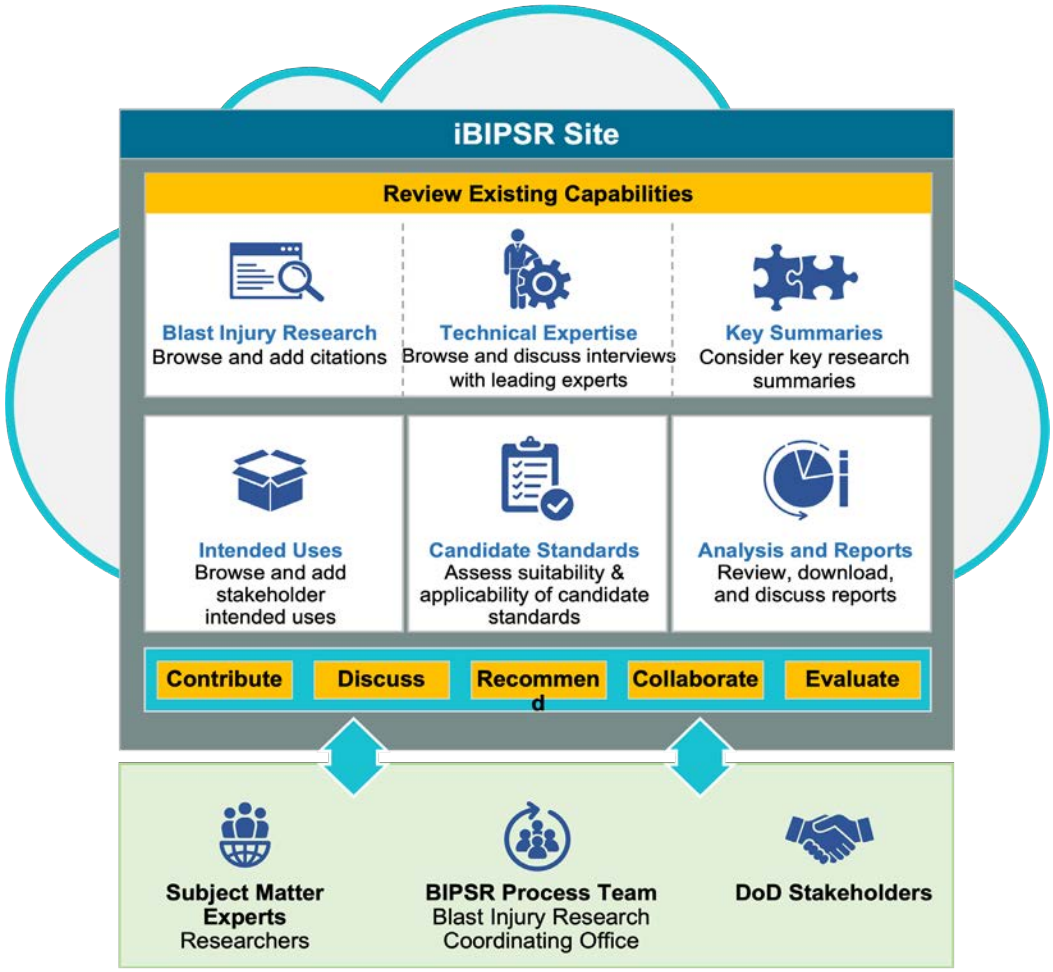
iBIPSR Capability

iBIPSR is an online forum developed to enhance information sharing among blast injury experts. iBIPSR supports BIRCO's EA mission to leverage existing knowledge and foster collaboration among academia, industry, international partners, and government organizations by providing a platform for continuous participation and maximum collaboration throughout the BIPSR Process.

As shown in Figure 3-3, the iBIPSR capability supports a variety of users engaged in planned collaborative interactions between and among BIPSR Process stakeholders, SMEs, BIRCO, and the MITRE team.

Photo credit: Pfc. Meshaq Hylton/U.S. Marine Corps

FIGURE 3-3: BIPSR Process supported by the iBIPSR site



Additionally, the iBIPSR capability offers transparency by capturing and managing stakeholder organizations' knowledge gaps and needs to facilitate understanding through near-real-time communication among participants. The MITRE team has developed the iBIPSR capability using best practices, established standards, and user input. iBIPSR will continue to evolve through user input to ensure it meets the knowledge goals of the mission.

MHS BIPSR Process Blast Injury Type Prioritization

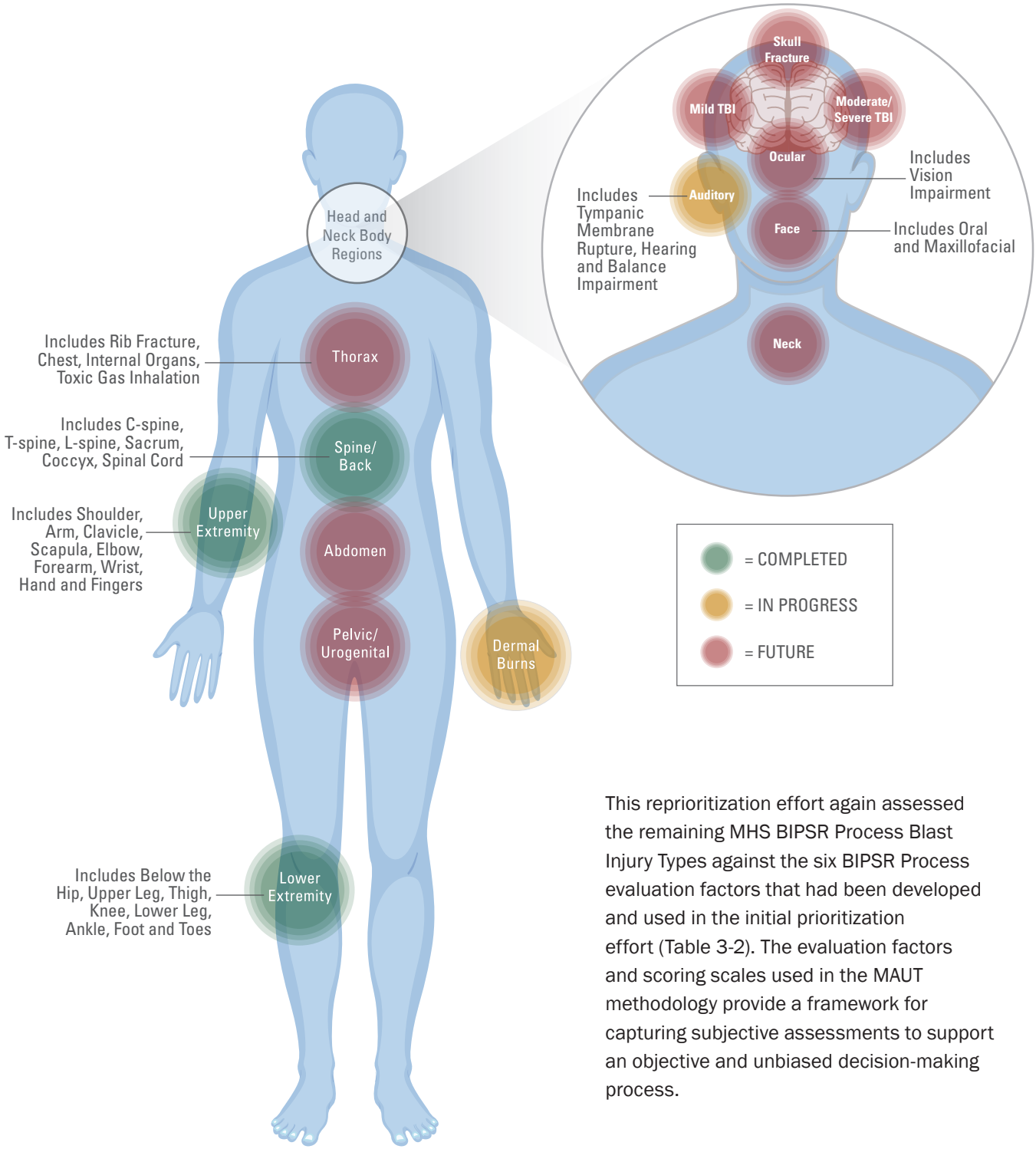
Through a series of initial BIPSR Process stakeholder meetings hosted by BIRCO, BIPSR Process stakeholders categorized 14 MHS BIPSR Process Blast Injury Types based on specific body regions (Figure 3-4). This represented a shift from an older classification of injury types that referred to individual organs and bones (as described in a 1989 report from the Walter Reed Army Institute of Research).

To identify the needs of the DOD, the BIPSR Process team determined the initial order for executing the BIPSR Process by applying a mathematical methodology, using stakeholder inputs, to establish a priority ranking of the Blast Injury Types. This Blast Injury Type prioritization methodology assessed and rated each MHS BIPSR Process Blast Injury Type against six evaluation factors developed by the BIPSR Process stakeholders and defined in Table 3-2. As of FY21, the Lower Extremity, Spine and Back, and Upper Extremity Blast Injury Types were complete; as of FY22, the BIPSR Process is underway for the Auditory and Dermal Burns Blast Injury Types. To meet the current needs of the operational environment and the DOD, BIRCO has performed a reprioritization effort for the remaining nine MHS BIPSR Process Blast Injury Types: ocular, face, neck, thorax, abdomen, pelvic/urogenital, skull fracture, mild traumatic brain injury (mTBI), and moderate/severe TBI. The reprioritization effort applied an established mathematical analysis technique, multi-attribute utility theory (MAUT), a widely used, widely accepted methodology for guiding tradeoffs among multiple objectives.

TABLE 3-2: BIPSR Process Evaluation Factors

Evaluation Factor	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 members' medical care
Maturity of the Science	Determined by the existence of established standards 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 (e.g., therapy, pharmaceuticals, and devices needed to reset for quality of life) required to support a Service member's rehabilitation beyond immediate treatment resources
Disability Percentage	The designated percentage assigned to an injury type when calculating disability benefits

FIGURE 3-4: Categorization of MHS BIPSR Process Blast Injury Types by Body Region



This reprioritization effort again assessed the remaining MHS BIPSR Process Blast Injury Types against the six BIPSR Process evaluation factors that had been developed and used in the initial prioritization effort (Table 3-2). The evaluation factors and scoring scales used in the MAUT methodology provide a framework for capturing subjective assessments to support an objective and unbiased decision-making process.

Throughout the effort, the MITRE team assessed the Blast Injury Types based on the evaluation factors by conducting extensive literature reviews to determine the maturity of the science and establish the resources required for rehabilitation, performing research to establish the impact on operational readiness, and evaluating resources for medical treatment. The MITRE team also worked with the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) to establish the relative prevalence and severity of each Blast Injury Type and collaborated with medical SMEs to analyze data on disability percentages.

BIPSR Process stakeholders provided inputs to the reprioritization process to ensure that the results reflect current DOD priorities.

In the final step of the exercise, a score was calculated using the MAUT methodology for each Blast Injury Type, resulting in a new rank order.

BIRCO shared the results of the reprioritization exercise at the BIPSR Process Stakeholder Committee Meeting #6. Table 3-3 shows the new recommended order for initiating future MHS BIPSR Process Blast Injury Types.

TABLE 3-3: Stakeholder recommended order for initiating future BIPSR Process Blast Injury Types

Blast Injury Type	New Rank Order
Skull fracture	1
Pelvic/Urogenital	2
Moderate/Severe TBI	3
Thorax	4
Abdomen	5
mTBI	6
Face	7
Neck	8
Ocular	9

Next Steps for MHS BIPSR Process Injury Type Prioritization

In FY22, BIRCO plans to reprioritize the BIPSR Process Blast Injury Types not yet completed or initiated to meet the DOD's highest priority needs. As in the previous exercise, the effort will include a literature review to determine the maturity of the science and establish the resources required for rehabilitation, research to establish the impact on operational readiness, evaluation of resources for medical treatment, coordination with the JTAPIC to establish the relative prevalence and severity of each Blast Injury Type, and collaboration with medical SMEs to analyze data on disability percentages.

BIPSR Process for the Auditory Blast Injury Type

The BIPSR Process for the Auditory Blast Injury Type is in progress and is an exemplar to prove the iBIPSR capability. As part of the initial steps of the BIPSR Process, the MITRE team completed the existing capabilities review of the Auditory Blast Injury Type: performing an in-depth literature survey, posting an RFI on the Federal Business Opportunities website (now SAM.gov), and interviewing SMEs from industry, academia, and government agencies. BIRCO also established the Auditory Focused Stakeholder Committee, comprising 14 members representing the U.S. Army, Navy, Air Force, Marine Corps, U.S. Department of Veterans Affairs, and the materiel development, operational, T&E, and medical communities of interest. The Auditory Focused Stakeholder Committee drives all major decisions for the BIPSR Process Auditory Blast Injury Type.

Summary of Work Before FY21

During the October 2016 Auditory Focused Stakeholder Committee Meeting, participants concurred with the MITRE team's recommendation to continue the BIPSR Process for the Auditory Blast Injury Type by convening a SME Panel of auditory experts to independently evaluate the existing capabilities.

Photo credit: Lance Cpl. James B. Novle/U.S. Marine Corps

BIRCO subsequently supported the assembly of the BIPSR Process Auditory SME Panel whose members are drawn from industry, academia, and government. Aligned with the BIPSR Process, these 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 IV&V.

The first meeting of the BIPSR Process Auditory SME Panel took place on September 19–20, 2017. The MITRE team introduced the SME Panel to the BIPSR Process, iBIPSR, and the findings to date; they then revised the intended uses of a candidate standard (which were provided by the stakeholders) and evaluation criteria in preparation for the independent candidate standards evaluation.

The second meeting of the BIPSR Process Auditory SME Panel was held on February 27, 2018. The MITRE team reviewed the candidate standard evaluation methodology, and the SME Panel reviewed the candidate standard evaluation methodology, and discussed and updated the evaluation factors. At the end of the meeting, the MITRE team provided information about the next steps in the BIPSR Process, including finalizing the Evaluation Factors.

During SME Panel Meeting #3 on July 31–August 1, 2018, the Panel reviewed its activities to date – the evaluation methodology and findings, evaluation criteria, and candidate standards – and finalized the evaluation materials. The SME Panel discussed topics influencing the relative importance of different Evaluation Factors and discussed information that would be needed about the candidate standards to complete the evaluation. The SME Panel established the weights and scoring levels that would be used to evaluate the candidate standards.

The fourth meeting of the SME Panel was held on November 27–28, 2018, and was followed by a series of six teleconference calls. Discussion during these meetings included detailed reviews of candidate standard information collected from

Photo credit: Airman 1st Class Natalie Fiorilli/U.S. Air Force

the literature and in coordination with candidate standard developers/champions, test cases, and datasets.

The SME Panel reviewed information for 14 candidate standards and identified questions for clarification from the candidate standard developers/champions. Candidate standard developers and champions provided written responses to the SME Panel that were discussed at the following SME Panel teleconference meeting. These meetings led to the completion of the candidate standard information documents on August 9, 2019.

Discussion of datasets and test cases resulted in the development of a list of datasets, along with the SME Panel usability assessment activity to investigate candidate standard usability and identify instances of high variability between candidate standards in predicted allowable number of rounds, which could be used to prioritize future research.

Early in FY20, the SME Panel reviewed and assessed the comprehensive information on identified candidate MHS Auditory Blast Injury Prevention Standards. They also reviewed existing datasets, identified knowledge gaps in existing auditory blast injury data, considered approaches for the upcoming evaluation of candidate standards, and discussed the development of a T&E plan to ensure the validity and biofidelity of the models. In support of the SME Panel's evaluation, the MITRE team developed and, in October 2019, finalized the usability assessment process for the Auditory Blast Injury Type.

The SME Panelists and candidate standard developers and champions completed the usability assessment in December 2019. Participants used the candidate standards to calculate the allowable number of rounds for five de-identified waveforms. MITRE analyzed the results then held a SME Panel meeting on March 13, 2020, to present findings and discuss the outcomes. This included discussion of the potential causes of variability in responses between SME Panelists and led to a consensus that allowed the BIPSR Process to progress. BIRCO also reviewed existing auditory blast datasets to identify data gaps (such as combined continuous and impulsive noise) and data that could potentially help support candidate standard assessments.

Industrial hygienists perform site assessments for noise to identify risks and inform mitigation decisions. Following collection on site, the data are often brought back to offices for analysis or sent to other organizations, such as the U.S. Army Public Health Center. Unfortunately, data collection is not a perfect science, and inconsistencies and environmental conditions can affect the utility of the data for evaluating noise hazards and informing mitigation strategies. Through discussions with the SME Panel, BIRCO identified the benefits of an anomaly detection system, which could be run on location to inform data collection on sites and optimize the utility of collected data. In 2020, BIRCO supported the development of this prototype software, called Automatic Waveform

Photo credit: Sgt. Alexis Flores/U.S. Navy

Anomaly Real-Time Detector (AWARD), to detect common data anomalies to inform appropriate use of data and identify any need for additional data collection. The approach was developed in MATLAB for the easiest transition to research and data acquisition communities following documentation and finalization of the tool.

The SME Panel then initiated their independent evaluation of each candidate standard using the evaluation factors. Over three meetings during April and May 2020, the SME Panel discussed questions related to the evaluation process and information on the standards, such as how limitations with collected waveforms (such as artifacts) affect the accuracy of candidate standards.

Developments in FY21

In FY21, BIRCO continued to direct the BIPSR Processes for auditory blast injuries. The SME Panel completed their evaluation of the candidate standards. BIRCO collated and analyzed the results for presentation and discussion with the SME Panel. BIRCO hosted a teleconference meeting on July 23, 2021, to discuss the next steps using the Delphi method-based approach for iterative discussion of the candidate standard evaluation findings to build consensus and support BIPSR Process recommendations.

The BIPSR Team from MITRE initiated the finalization and documentation of the AWARD tool.

Next Steps for the Auditory Blast Injury Type

A series of meetings are planned to include the SME Panel discussion of detailed findings from the candidate standards evaluation process and the development of a draft auditory blast injury prevention standard recommendation for consideration by the BIPSR Process stakeholders. As the next step, a Consensus Building Meeting is planned for FY22 involving stakeholders, candidate standard developers, academia, industry, and government SMEs to share findings and allow for discussion and final development of the auditory blast injury prevention standard recommendations, and identify remaining knowledge gaps for dissemination to the research community. The DOD EA in turn plans to submit the recommended Auditory blast injury prevention standard recommendations to the ASD(HA).

Additionally, in FY22 BIRCO plans to finalize and release the AWARD tool for use by the community. This prototype software supports the detection of common data anomalies (e.g., microphone clipping, low signal to noise ratio, and DC shift) to inform appropriate use of data and identify any need for additional data collection.

Initial use and findings suggest that AWARD will benefit the community by helping to identify anomalies in real time to maximize the utility of data collection efforts. AWARD does not currently identify all potential issues with waveform data that could assess utility for noise hazard assessment but is a starting point that can be expanded by BIRCO and/or the auditory research community, to detect a wide breadth of waveform anomalies.

BIPSR Process for Dermal Burns Blast Injury Type

The BIPSR Process for the Dermal Burns Blast Injury Type has been initiated per the recommendation of the BIPSR Process stakeholders, and the existing capabilities review is in progress. The existing capabilities review will capture the activities and findings shared with Dermal Burns Focused Stakeholders Committee and SMEs for review and feedback throughout the BIPSR Process. Early activities included a literature review and identification of Dermal Burns SMEs for interviews to inform the existing capabilities review. Several SMEs from industry, academia, and government agencies have been interviewed, with additional SMEs to be interviewed in FY22 to ensure the state of the science is understood and captured.

Impacts from the COVID-19 pandemic delayed completing SME interviews, establishing the full Dermal Burns Stakeholder group, and convening for a kickoff meeting, which is now planned for FY22.

Next Steps for Dermal Burns Blast Injury Type

BIRCO plans to convene the Focused Stakeholder Committee for the BIPSR Process and prepare an RFI to achieve the following:

1. Obtain information on existing dermal burn blast injury criteria, thresholds, standards, models, etc., that could be considered as potential DOD standards, as well as those being developed or researched that could inform the BIPSR Process
2. Identify gaps between existing knowledge and knowledge needed to inform standards
3. Give performers/producers of existing protection systems relevant to understanding human tolerance limits and predicting injuries sustained by blast victims an opportunity to describe how they can assist in standards identification, development, and research
4. Identify researchers who are invested in blast injury criteria, thresholds, and testing methods and who possess appropriate scientific expertise, experience, and resources to describe and provide the scientific evidence needed to inform the standards
5. Identify and obtain methodologies, tools, models and simulations, dose-response curves, injury thresholds, computational models, their components and parameters, and associated technologies that may contribute to an upgradable platform for continuous integration of improved technologies
6. Obtain information from a broad community, including industry, academia, and other federal agencies on the availability of military-relevant blast injury standards

Following the issuance of the RFI, BIRCO will conduct and coordinate interviews with the Dermal Burns Focused Stakeholders Committee to characterize intended uses and requested

Photo credit: Pvt. Paulina Castaneda/U.S. Army

functionalities for an MHS Blast Injury Prevention Standard for Dermal Burns. BIRCO will also conduct SME interviews to ensure a thorough understanding of the current state of the science. These SME interviews will help identify dermal burns blast injury criteria that may be suitable as a potential DOD dermal burns standard and related ongoing research. An analysis of the current state of the science and the intended uses against identified candidate standards will inform the next steps in the BIPSR Process for Dermal Burns. These next steps will include identification of functionalities of a dermal burns injury standard, priorities for dermal burns standard development, and identification of possible research gaps to be targeted.

Way Forward

Ultimately, the knowledge gaps revealed 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. The science and technology knowledge gaps identified for MHS BIPSR Process Blast Injury Types will be shared with the medical research community to inform the development of future MHS Blast Injury Prevention Standards.

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Photo credit: LCpl. Darien Bjorndal/U.S. Marine Corps

CHAPTER 4:

NDAA SECTION 734 BLAST OVERPRESSURE STUDY

Longitudinal Medical Study on Blast Pressure Exposure of Members of the Armed Forces

Service Member Focus

Over time, significant advancements have been made to support the risk mitigation and treatment of Service member blast injury. While materiel solutions have helped address some effects of blast pressure exposures, the 2018 Center for a New American Security report "Protecting Warfighters from Blast Injury" documented concerns about blast pressure exposures from weapon systems on Service member health and performance. Service members experience blast exposure during training and combat, affecting force lethality, readiness, and individual long-term health outcomes. It is known that high magnitude blast overpressure can result in lung damage and tympanic membrane rupture. However, there are questions about low-level blast exposure effects, such as exposures when training on weapon systems and cumulative effects from career exposures.

Interest from both the public and private sectors resulted in the National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2018, Public Law 115-91, Section 734, which requires that the Secretary of Defense conduct a longitudinal medical study on blast pressure exposure of members of the Armed Forces during combat and training. On October 1, 2018, the Deputy Secretary of Defense signed the memorandum "Comprehensive Strategy and Action Plan for Warfighter Brain Health," calling for a comprehensive plan comprising research, surveillance and prevention, diagnosis, treatment, rehabilitation and reintegration, outreach education, and training (see Figure 4-1 for reporting elements). This memorandum established the Warfighter Brain Health (WBH) Initiative, of which the NDAA Section 734 Program is a component.

FIGURE 4-1: Reporting Elements of FY18 NDAA, Public Law 115-91, Sec. 734

1. Monitor, record, and analyze data on blast pressure exposure for any member of the Armed Forces who is likely to be exposed to a blast in training or combat;
2. Assess the feasibility and advisability of including blast exposure history as part of the service record of a member, as a blast exposure log, in order to ensure that, if medical issues arise later, the member receives care for any service-connected injuries; and
3. Review the safety precautions surrounding heavy weapons training to account for emerging research on blast exposure and the effects of such exposure on cognitive performance of members of the Armed Forces.

NDAA Section 734 Program Authorization Organization

In FY18 NDAA, Public Law 115-91, Section 734, Congress directed the Secretary of Defense to conduct a longitudinal medical study on blast pressure exposure of members of the Armed Forces. Subsequent legislation expanded on that mandate, including FY19 NDAA, Public Law 115-232, Sec. 253 of the John S. McCain National Defense Authorization Act for Fiscal Year 2019, which required a review of the guidance on blast pressure exposure during training; FY20 NDAA, Public Law 116-92, Section 717, which required the inclusion of blast exposure history in medical records of Service members; and FY20 NDAA, Public Law 116-92, Section 742, which added to the requirements for the longitudinal study directed by FY18 NDAA, Public Law 115-91, Section 734.

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

The NDAA Section 734 Program involves contributions from blast engineers, munitions testing and operational personnel, safety officers, health care providers, clinical researchers, and others to offer a comprehensive approach to interpreting blast exposure data and developing recommendations for enhancing blast exposure safety in training and operational environments. The Principal Deputy of the Office of the Assistant Secretary of Defense for Health Affairs (OASD(HA)) established the Section 734 Workgroup to develop a targeted strategy to address the Congressional requests, promote collaboration across the Services' lines and medical communities, and reduce duplication of effort. Section 734 Workgroup members from 54 organizations across the DOD, Services, and U.S. Department of Veterans Affairs (VA) helped establish the program structure and scope.

NDAA Section 734 Program Goals and Scope

The goal of this initiative is to successfully conduct a series of studies (i.e., examination of health and performance effects) of blast pressure exposure of members of the Armed Forces during combat and training, including Service members who train with high overpressure weapon systems. These systems include anti-tank recoilless rifles or heavy-caliber sniper rifles and inform training and operational safety doctrine, protocols, and policies to best protect Service members. The scope of the initiative includes a series of studies and assessments to achieve the goal rather than a single longitudinal study. This multiple study methodology will capture answers to lines of inquiry that would prove challenging to accomplish with one large and unwieldy study and enable more opportunities for success. The initiative builds on existing work and requires a portfolio of studies that will support all reporting elements. The results from the portfolio will inform safety standards and medical policy to protect Service members' health. Additionally, the studies will address the feasibility of tracking and documenting blast exposures during a Service member's career lifecycle.

> The goal of the NDAA Section 734 Program is to improve the DOD's understanding of the impact of blast pressure exposure from weapon systems on Service members' brain health and to inform policy for risk mitigation, unit readiness, and health care decisions.

Selection of Priority Tier 1 Weapon Systems for Study

A February 2019 memorandum required the Secretaries of the Military Departments to identify their top 3–5 high overpressure weapon systems that generate blast pressure exposure effects for Service members and the military occupational specialties of those personnel at greatest risk to blast exposure from high overpressure weapon systems. The memorandum also required identification of training events or venues where the selected systems are routinely employed and those feasible for inclusion in the study. A resulting list of Tier 1 weapon systems was established by OASD(HA) as a priority for the program and is shown in Figure 4-2.

FIGURE 4-2: NDAA Section 734 Program–Priority Tier 1 Weapon Systems

Program Structure

Lines of Inquiry and Responsibilities

The OASD(HA) and the Section 734 Workgroup developed a program structure to facilitate additional detailing of the study methods and action plan. The program structure (Figures 4-2 and 4-3) identifies organizations that provide oversight, guidance, and coordination; and that promote translation of study findings to the Services. The program structure includes five Lines of Inquiry (LOIs) – Surveillance, Weapon Systems, Exposure Environment, Blast Characterization, and Health and Performance – to support the three reporting elements of FY18 NDAA, Public Law 115-91, Section 734.

An Office of Primary Responsibility (OPR) leads each LOI and is responsible for the operational management of the work. Figures 4-4 and 4-5 show the five LOIs and their OPRs, along with the overall program structure of the NDAA Section 734 Program effort.

The Surveillance LOI assesses the feasibility and advisability of including blast pressure exposure history in the service and/or medical records of members of the Armed Forces, pilots the implementation of a personnel monitoring surveillance program, and analyzes data to improve understanding of blast pressure exposures of members of the Armed Forces.

The Weapon Systems LOI coordinates, collates, and analyzes information on blast pressure resulting from heavy weapons and blast events and will inform strategies to account for emerging research on the effects of blast pressure exposure on the health and performance of members of the Armed Forces.

FIGURE 4-3: DHA is Leading a Collaborative and Unified Response

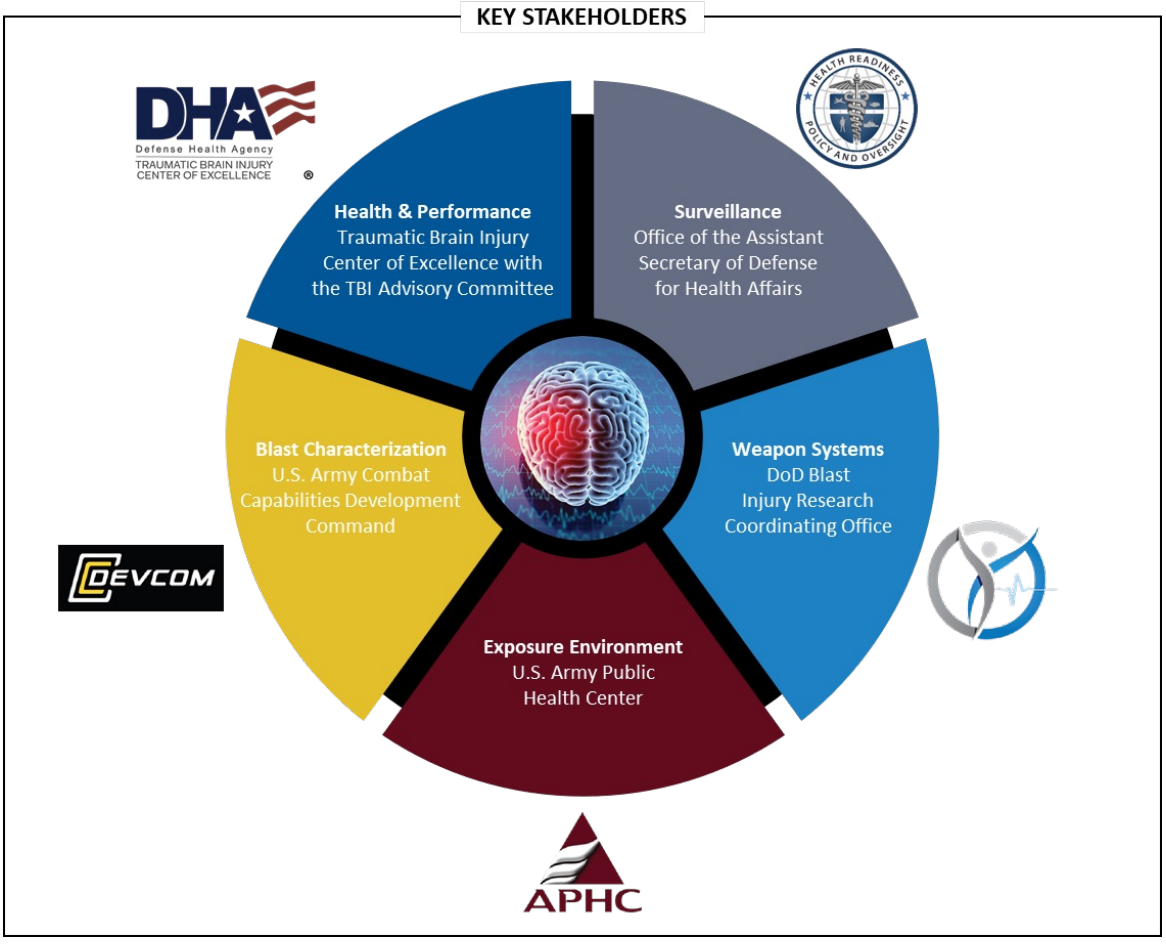


FIGURE 4-4: NDAA Section 734 Program Structure

Health and Performance LOI 5: Traumatic Brain Injury Center of Excellence (TBICoE) formerly named the Defense and Veterans Brain Injury Center (DVBIC), aligns with the other centers of excellence within the Defense Health Agency's Research and Development Directorate.

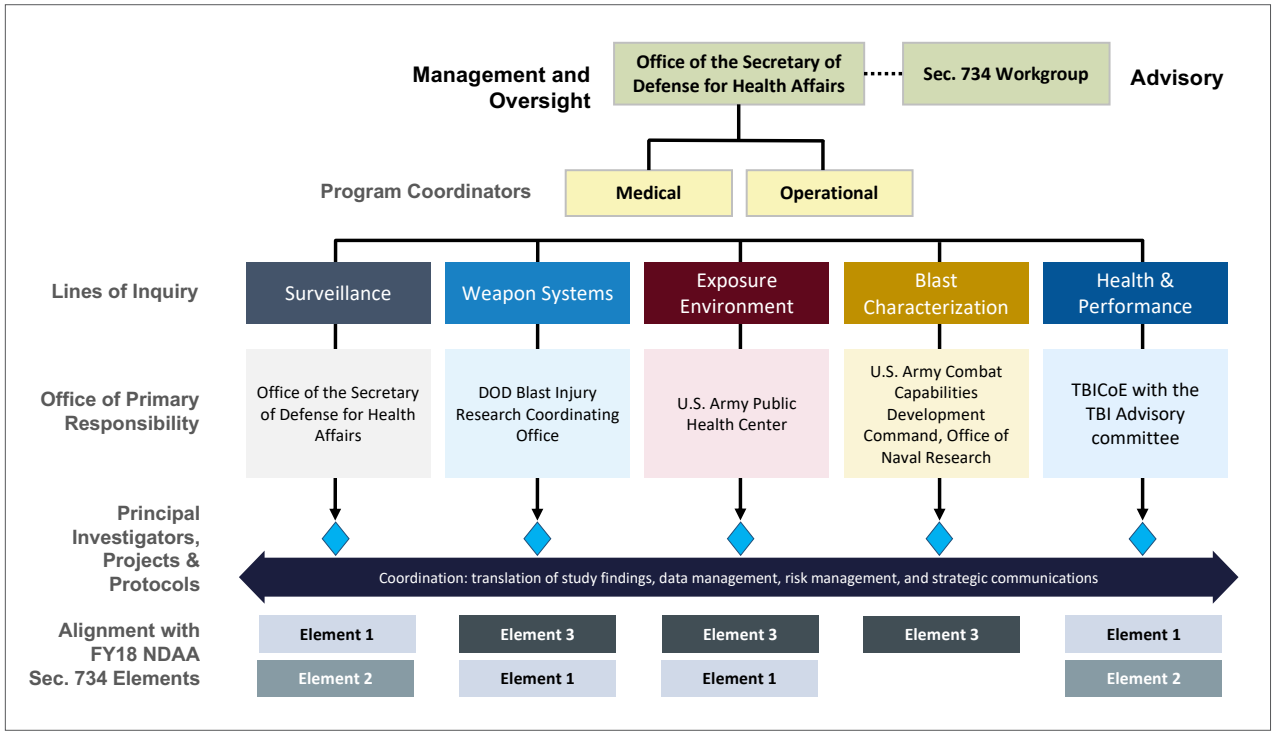
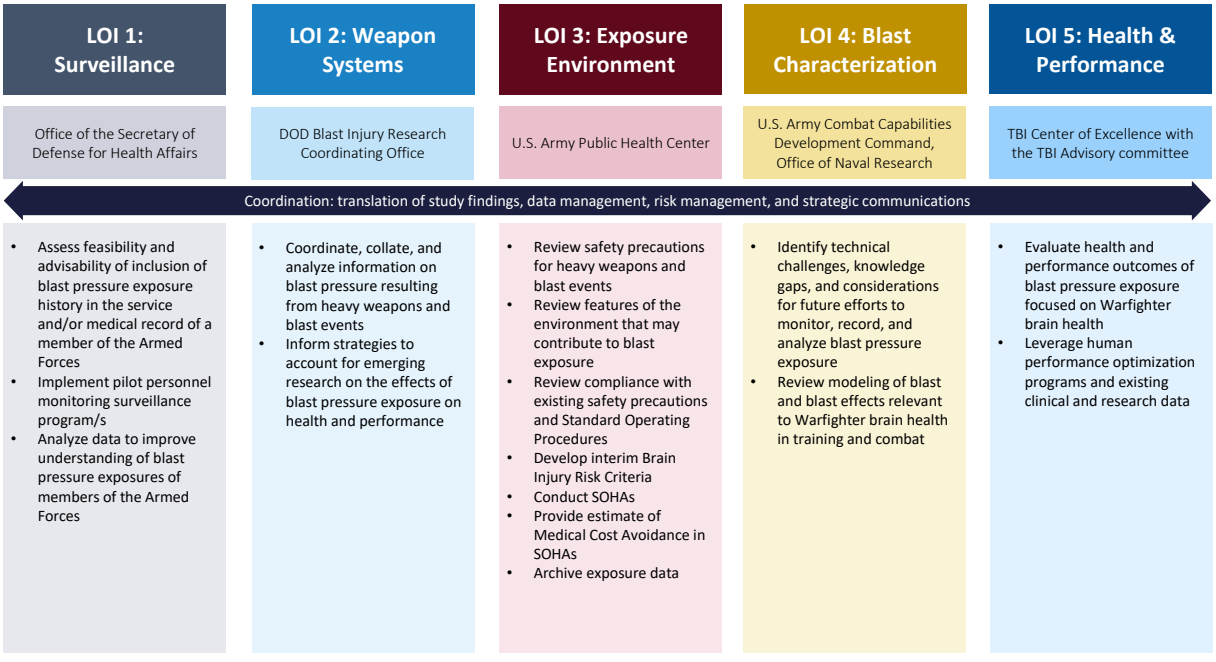


FIGURE 4-5: FY18 NDAA Sec. 734 Program LOI



The Exposure Environment LOI reviews safety precautions for heavy weapons and blast events in different blast environments. The features of the environment may contribute to blast exposure-related changes in the health and performance of members of the Armed Forces, and compliance with existing safety precautions and Standing Operating Procedures.

The Blast Characterization LOI reviews the modeling of blast and blast effects relevant to Service members' brain health in training and combat and will identify technical challenges, knowledge gaps, and considerations for future efforts to monitor, record, and analyze blast pressure exposure.

The Health and Performance LOI evaluates health and performance outcomes of blast pressure exposure focused on Service member brain health by leveraging human performance optimization programs and existing clinical and research data.

Accomplishments and Ongoing Efforts

The next sections outline the accomplishments and ongoing efforts for each LOI during fiscal year (FY) 2021. To achieve their objectives, efforts covered a variety of activities, including research, data gathering, analysis, and software prototyping. In addition, the teams routinely presented their work in various forums to ensure collaboration and timely information sharing.

LOI 1: Surveillance

The OPR is the OASD(HA). It assesses the feasibility and advisability of including blast pressure exposure history in the service and/or medical record of members of the Armed Forces, piloting the implementation of a personnel monitoring surveillance program, and analyzing data to improve understanding of blast pressure exposures of members of the Armed Forces.

Central to the longitudinal medical study requested by FY18 NDAA, Public Law 125-91, Sec. 734 is an assessment of the feasibility and advisability of including blast overpressure exposure history in the service and/or medical records of members of the Armed Forces. Presently, the DOD and VA depend almost entirely on self-reported accounts of blast overpressure exposure and/or presumptive exposures from training and combat scenarios. Therefore, the DOD and VA seek an individual longitudinal record of blast overpressure exposure to ensure that service-connected blast exposure health and performance effects are accurately and adequately addressed, even if medical issues arise later.

OASD(HA) has directed a three-phase pilot program of blast overpressure exposure monitoring and surveillance (termed Blast Overpressure Studies–Pilot (BOS-P)) to assess the feasibility of Service-wide implementation. The three phases are outlined below.

1. The BOS-de-identified (BOS-D) phase will utilize previously collected blast exposure data as a template to design the data infrastructure required to process and store blast exposure records.
2. The BOS-Surveillance (BOS-S) phase will employ the Neuro-Tactical Research Team from the Uniformed Services University of the Health Sciences (USUHS) to execute blast overpressure exposure monitoring of infantry units during single-day, live-fire training of Tier 1 munitions. BOS-S aims to emulate intensive exposure monitoring by documenting blast-relevant contextual metadata variables such as body positioning, personal protective equipment, barometric pressure, reflectance source, and the blast overpressure waveform data from body-mounted sensors.
3. The BOS-Longitudinal (BOS-L) involves the three-to-four month issuance of blast gauges to simulate an enduring program of record.

Modification of the BOS requirements outlined in FY20 NDAA, Public Law 116-92, Sec. 742 specified the electronic data systems into which blast overpressure exposure data must be stored and the desired technical capabilities therein. In addition, the legislation included uploading collected data into DOD industrial hygiene and health care databases, namely the Defense Occupational and Environmental Health Readiness System – Industrial Hygiene (DOEHRS-IH), Individual Longitudinal Exposure Record (ILER), and Genesis Medical Health System (MHS Genesis).

The three phases of BOS-P collectively provide the framework to assess Service-wide feasibility per the Congressional mandate. The BOS-P effort will outline the capabilities, limitations, and technical requirements for the collection, storage, and management of individual blast exposure data.

Accomplishments

BOS-D completed the upload and transfer of de-identified (i.e., without personal identifiers) blast overpressure exposure data into the DOEHRS-IH and ILER electronic systems. Raw data from the blast gauges were signal-processed and configured for storage within DOEHRS-IH where the ILER system may query individual exposure records.

Personally identifiable blast overpressure exposure data have been collected through BOS-S and BOS-L work with the 2nd Brigade Combat Team (2 BCT) of the 101st Airborne Assault Division (AASLT) at Fort Campbell, Kentucky. The weapon systems used during these training events are highlighted in yellow in Figure 4-6. USUHS Operation Managers (OMs) have gathered exposure records from more than 320 Service members, including 45 contextual data elements for 88 individual members for BOS-S, and three months of continuous surveillance records for 233 Service members for BOS-L. Service members also completed a survey addressing the impact of each of the elements from doctrine, organization, training, materiel, leadership and education, personnel, facilities, and policy (DOTMLPF-P).

FIGURE 4-6: Weapon Systems Identified by the Secretaries of the Military Departments as high priority regarding blast generation. Munitions in yellow have been recorded during BOS-P activities at Fort Campbell.

Future Plans

The team continues to oversee the processing of personally identifiable BOS-P exposure data and additional pilot monitoring and surveillance of Service members. Investigators from Yale University and Applied Research Associates, Inc. (ARA) are developing the computing tools necessary to automate high-throughput processing of raw blast gauge data, including estimation of a single incident overpressure waveform, quality assurance of recorded events, configuration for ingestion into DOEHRS-IH, and automated generation of a batch-based unit-level Commander's Report. Demonstration of exposure data collection integration with DOEHRS-IH, ILER, and MHS Genesis will be a major milestone for the BOS effort.

Additionally, the team is arranging to extend BOS S and BOS L operations to the Marine Corps' Range Safety Officers and units from 1st Battalion 7th Marines at Twentynine Palms, California to

document Service-specific implications for an enduring blast overpressure exposure program of record. Operational and technological implications learned from the BOS-P pilot program will generate recommendations to meet FY18 NDAA, Public Law 115-91, Section 734 requirements.

LOI 2: Weapon Systems

The OPR is BIRCO. BIRCO coordinates, collates, and analyzes information on blast pressure resulting from heavy weapons and blast events. In addition, BIRCO informs strategies to account for emerging research on the effects of blast pressure exposure on the health and performance of Service members. BIRCO focuses on developing an improved understanding of the blast exposures resulting from firing or detonating various weapon systems by evaluating existing documentation of the weapon systems in development, testing, training, and modification scenarios. In addition, the Office analyzes the way these exposure components are described and captured in research, testing, and training communities.

Accomplishments

The team has been conducting activities to assess and review safety precautions surrounding heavy weapons, often coordinating with other LOIs. Their work resulted in a refined and updated action plan, which was developed to assess and review the safety precautions surrounding heavy weapons in training to account for emerging research on blast exposure and the effects of blast exposure on the cognitive performance of members of the Armed Forces.

LOI 2 efforts have included collecting information; leveraging existing work on Tier 1 weapon systems characterization and methodologies; conducting a review to evaluate consistency; analyzing data for relevancy, accuracy, and quality; and documenting findings (e.g., differences, inconsistencies, practices) that could affect safe weapon systems use in training and combat. Existing work leveraged includes documents such as the Range Safety DA-PAM, Range Manager Toolkit (RMTK), Technical/Operational manuals, Industry flyers, training circulars, training materials, and weapon use information. The analysis has identified gaps and variability in safety guidance across the Services (e.g., weapons use conditions, Allowable Number of Rounds [ANOR]) and inconsistent terminology for safety concepts, such as ANOR.

Early on, the team recognized the need to house key pieces of information related to the use of heavy weapons systems to facilitate the FY18 NDAA, Public Law 115-91, Section 734 effort. To address this need, LOI 2 and LOI 3 teams collaborated to establish a Tier 1 weapon systems information prototype database. For each weapon system, the database includes elements such as the following:

- Most commonly fired round
- ANOR, by pose and type of round (updated as Health Hazard Assessments [HHAs] are performed)
- Round of most concern
- Required safety precautions (e.g., hearing protection, standoff distance)
- Detailed testing methodologies
- Training information

The database information was then used to develop draft executive summaries (EXSUMs) of key data for select Tier 1 weapon systems, which have provided a consolidated reference for the NDAA Section 734 Program.

New Capability, Blast Overpressure Tool Module

A review of the RMTK suite of tools, designed to automate range operations, modernization, and safety tasks, revealed that none of the current tools provide blast overpressure exposure information. As a result, a new capability, a prototype Blast Overpressure Tool module, is being developed for integration into the RMTK and as a stand-alone tool module. This new capability to develop a RMTK Blast Overpressure Tool module

is adapting the CoBi-Blast solver to predict blast overpressure loads on Service members involved in heavy weapons training.

The team has improved and modified the CoBi-Blast tool for reconstruction of selected Tier 1 weapon system training scenes and initiated the testing, refinement, and validation of the tool by collecting specific data during weapon system training under operational conditions. These field validation studies involve collecting data — such as high-resolution blast waveforms, positioning of individuals relative to the blast source, atmospheric conditions, and characteristics of surrounding reflective surfaces — to generate simulations of blast wave propagation and blast pressure loading on individuals. A validated RMTK Blast Overpressure Tool will improve the understanding of Service member blast exposure and will inform safer protocols for repeated blast exposure in training. LOI 2 is collaborating with Walter Reed Army Institute of Research (WRAIR) for these data collection activities required to validate, test, and refine the prototype RMTK Blast Overpressure Tool module. For this initial data collection and validation effort, the prototype includes a subset of four Tier 1 weapon systems, listed and pictured in Figures 4-7, 4-8, 4-9, and 4-10 below.

- Shoulder-mounted: M136 (AT4)
- .50 caliber weapons: Sniper rifles M107 and MK15
- Indirect Fire Systems: M120/M121 120mm
- Breaching Charges

LOI 2 convened an integration team with technical subject matter experts (SMEs) from CFD Research Corporation (CFDRC), WRAIR, MITRE, and BIRCO,

FIGURE 4-7: 76 AT4 Launch
(Photo by Sgt. Marcus Fichtl 2nd Brigade Combat Team, 4th Infantry Division Public Affairs)

FIGURE 4-8: M240B and M107 Live Fire Range
(Photo by Sgt. Manuel Serrano)

FIGURE 4-9: 2nd Battalion, 108th Infantry Regiment mortar crews qualify
(Photo by Matthew Day Watervliet Arsenal)

FIGURE 4-10: Breaching
(Photo by Cpl. Teagan Fredericks Task Force 51/5th Marine Expeditionary Brigade)

as well as RMTK experts, to support the Blast Overpressure Tool module integration efforts in to the RMTK. In addition, the team continues evaluation, support and refinement, and an independent assessment of the prototype module.

Blast Injury Threshold Review

A collaborative effort among LOIs 2, 3, and 5 led to the completion of the draft Blast Injury Threshold Review. The review summarized current information on repeated low-level exposure thresholds for brain injury, limitations to that information, and ongoing efforts to potentially close critical knowledge gaps. Key findings from the literature review identified a range of primary blast injury prevention thresholds in use across the DOD; however, the thresholds were not designed to prevent brain injuries.

Future Plans

The interim findings and continued assessment of documents provide insight into the state of the science, emerging research, weapon system safety guidance, knowledge gaps, and data gaps. This information will be used to inform recommendations on refining requirements during research, development and testing of weapon systems, training, personal protective equipment, strategy, safety standards, medical policy, and guidance with the ultimate goal of promoting safe Service member use of weapon systems in training and in combat. In addition, efforts indicate opportunities to improve communications of expected blast overpressure exposures in DOD policy and safety guidance. As new data are collected throughout the FY18 NDAA, Public Law 115-91, Section 734 effort, the Tier 1 Weapon System EXSUM will be updated, and the findings, analysis, and recommendations will be captured in a capstone technical report.

The draft Blast Injury Threshold Review report findings and recommendations will be developed and shared more broadly through DOD channels to support communications to the operations and safety community in order to support health and performance outcomes of Service members. Ongoing efforts seek to inform the extent of low-level blast exposures, health effects, and mechanisms of injury.

The Blast Overpressure Tool module integration team will continue to collaborate with technical SMEs and performers to identify integration requirements and develop an execution plan. The validation, testing, and refinement of the initial subset of Tier 1 weapon systems will be completed, and the prototype is expected to demonstrate an integration capability with RMTK. Additionally, as a part of the ongoing prototype Blast Overpressure Tool module efforts, parametric studies are planned to demonstrate capabilities around modifying individual postures and positions to potentially reduce instructor BOP exposure in training. The RMTK Blast Overpressure Tool module enhances DOD capabilities to communicate Service member blast overpressure exposure while using, or near, selected weapon systems. A validated RMTK Blast Overpressure Tool will improve understanding of Service member blast exposure and will inform safer protocols for repeated blast exposure in training. This information can guide decisions regarding training practices and injury risk tolerance, such as firing lane distances and ANOR.

LOI 3: Exposure Environment

The OPR is U.S. Army Public Health Center (APHC). The APHC has been tasked with helping to improve the DOD's understanding of the impact of weapon system-related blast overpressure exposures on Service members' brain health and determining how the environments in which these exposures occur affects Service members.

As the OPR for LOI 3, the APHC is responsible for meeting the following seven objectives:

1. Review safety precautions for weapons, breaching charges, and events in different blast environments.

2. Review compliance with existing safety precautions and standard operating procedures.
3. Review features of the environment that may contribute to blast overpressure-related changes in health and performance.
4. Develop Interim Brain Injury Risk Criteria for use with HHAs and Joint Service Member Occupational Health Assessments (JSOHAs) in accordance with Military Standard 882E.
5. Conduct JSOHAs on Tier 1 weapon systems and breaching charges.
6. Estimate medical and lost time cost avoidance through the Medical Cost Avoidance Model (MCAM).
7. Archive exposure data collected during JSOHAs in Service member records (e.g., DOEHRS-IH).

The JSOHA program (as it relates to assessing weapon systems) is complementary to and modeled after the HHA program at the APHC, which focuses on assessing weapon systems using data collected at Army test centers (pre-fielding). The JSOHA program assesses actual Service member exposures using data collected by personal exposure monitoring equipment and instrumentation (post-fielding). Each JSOHA conducted involves the following:

- An extensive assessment of existing safety precautions for the weapon system being sampled
- A review of how the operational environment affects the way the weapon system can be used and the Service member exposures
- An analysis of compliance with the reviewed safety precautions as the exercise is being observed
- The collection of blast overpressure, impulse noise, and chemical substances data using wearable instrumentation
- The completion of a JSOHA report split into sections to discuss findings and recommendations associated with each objective

Accomplishments

The APHC's LOI 3 team has adapted the JSOHA program to serve as the foundational component in accomplishing all objectives.

To date, JSOHAs have been conducted on the following Tier 1 weapon systems and breaching charges: M2A1 Browning machine gun, 81 millimeter (mm) mortar system, and wall, door, and fence breaching charges. JSOHAs on remaining Tier 1 weapon systems are planned for FY22. It is important to note that the APHC's current process for assessing blast overpressure is based on the risk of lung injury; however, efforts to develop processes to assign the risk of adverse brain health outcomes based on blast overpressure are underway. Below is an overview of the team's accomplishments associated with lung injury-related blast overpressure assessments.

The team performed lung injury-related blast overpressure analyses on eight weapon systems/test events during FY21. These analyses support the HHAs, or consultations associated with each materiel item. Blast data produced by spherical charges, as well as data from the following weapon systems, were assessed to determine their lung injury-related blast overpressure effects: the Hellfire R9E buried ordnance (two separate test events); the Mark 84 buried ordnance (two separate test events); the Mark 82 buried ordnance; the GBU-39/B Small Diameter Bomb Increment I buried ordnance; and the Multi-Target 756 Cartridge for the Multi-Role Anti-Armor Anti-Personnel Weapon System. Each of these weapon systems or munitions provides a unique capability to produce large blast events designed to enhance the lethality of Service members and protect them during combat.

Blast overpressure data were collected for each weapon system to determine the blast exposure to operators. The data were collected at Fort Polk, Louisiana, and U.S. Army Aberdeen Test Center (ATC), Maryland, with blast test devices (BTDs) at

Photo credit: Matthew Day/U.S. Marine Corps

crew positions simulating personnel location during firing/detonation events. Different conditions were tested for each weapon system using variations in charge, elevation, line of fire, round conditioning temperature, firing postures, munition burial depth, soil type, and location of the blast event, depending on the properties of the weapon system.

These data were then analyzed using the blast overpressure-HHA software version 2.1 and 3.0, depending on the type of data requested. U.S. Army Medical Research and Development Command (USAMRDC) developed this software under a contract with JAYCOR Corporation (now L-3 Applied Technologies Incorporated). The software is undergoing an update, with expected completion in FY22. It uses an algorithm based on a biomechanical model of the thorax that calculates the amount of irreversible mechanical work imparted to the thorax by a blast pressure wave, based on pressure-time data from BTDs. The algorithm calculates effective normalized work values and associates these values with the risk of lung injury outcomes based on dose-response curves developed from data collected from more than 1300 blast-exposed animal specimens. The analysis results in estimated lung injury risk (hazard severity and hazard probability) for different hazard levels and associated ANOR determinations, representing the number of exposures that will produce a less than one percent incidence of any lung injury within 24 hours. The ANOR and quantitative probabilities of lung injury for all lung injury severity levels were determined for each condition and crewmember position tested by Fort Polk and ATC. Ultimately, the software-generated hazard severity and hazard probability are used to assign a risk assessment code and resultant risk level to each weapon system for blast overpressure exposure.

Additionally, data collected by ATC was analyzed from BTDs positioned in a symmetrical arena around various sized C-4 and Pentolite charges in both indoor and outdoor environments. These data were collected to validate various BTD sizes and

configurations. The data were assessed in the field during collection and is also undergoing further analysis.

The APHC publishes most blast overpressure analyses in the HHA Reports used by Safety and Occupational Health professionals during the acquisition process. Other analyses are conducted on a consultative basis and provided to customers via a report or email depending on the request. The APHC expects the relevant blast overpressure analysis results to be included in training materials and operator manuals relevant to the materiel items/systems that were evaluated, which will enable Commanders to make better-informed decisions regarding training.

Additional major accomplishments include the following:

- Facilitation of contracts to update the blast overpressure-HHA software to validate various sizes and configurations of BTDs and to perform a Verification, Validation, and Accreditation of the MCAM
- Hosting of a Blast Overpressure Exposure Monitoring and Surveillance Program Planning Meeting
- Submission of a DOEHRS-IH New Investment Business Use Case and Concept of Operations for blast-related fields, batch data loading, and viewing capabilities
- Inclusion of a requirement for Army Futures Command to archive blast data in the submitted update of AR 40-10 (HHA's governing document)
- Establishment of the Blast-Related Brain Injury Interim Health Protection Criteria Working Group (HPC WG)

Future Plans

The team will conduct JSOHAs on all remaining Tier 1 weapon systems and breaching charges. Complete the efforts associated with updating the blast overpressure-HHA software, the validation of various sized BTDs, and the MCAM will be completed. The Blast-Related Brain Injury Interim HPC WG will meet regularly to finalize processes and methodologies to assess the risk of adverse brain health outcomes due to blast overpressure exposure. A requirement for Army Futures Command to archive blast data in AR 40-10 is expected to be established; requested updates are pending final approval. Efforts will be conducted to establish an HHA Center of Excellence requirement. The DOEHRS-IH New Investment will continue to be facilitated. An enduring and enhanced APHC Blast Overpressure Exposure Assessment Capability will continue to be developed.

LOI 4: Blast Characterization

The OPRs are the U.S. Army Combat Capabilities Development Command (DEVCOM) and the Office of Naval Research (ONR). These offices review modeling of blast and blast effects relevant to Service members' brain health in training and combat and identify technical challenges, knowledge gaps, and considerations for future efforts to monitor, record, and analyze blast pressure exposure. The team is focused on three areas, in collaboration with the other LOIs: repository development and toolset integration, computational modeling, and automation and analysis.

The team supports the identification of technical challenges, knowledge gaps, and considerations for future efforts to monitor, record, and analyze blast pressure exposure, including methods to evaluate blast exposure data quality prior to inclusion in records, modeling of blast effects, and recommendations for long-term data storage. The team is piloting capabilities and providing recommendations for developing an enduring DOD

Photo credit: Sgt. Timothy Hamlin/U.S. Army

capability for the longitudinal examination and derivation of weapons-based effects (existing and emergent) on Service members' brain health and performance.

Accomplishments

The team evaluated various technologies to realize the planned data storage capability in a scalable and extensible way by studying past high-performance computing developments and the latest data warehousing architectures. This effort resulted in system design and in selecting and implementing appropriate software components. Another team task demonstrated initial automated analysis capabilities with a small dataset that could be used in the future to support big data analytics on blast exposure effects.

The fast automated signal transformation for combat training (FAST-CT) capability will automate B3 sensor data analysis to remove spurious data to provide accurate standardized blast exposure metrics (e.g., incident impulse, incident peak overpressure). Applied Research Associates delivered the Alpha version of the FAST program. This work will help support the inclusion of accurate blast exposure data in Service members' records.

LOI 4 identified the following gaps across each of its focus areas:

1. There is a lack of standardized validation and verification processes as well as a lack of data quality screening.
2. Storage of key data elements used by multiple communities of interest (weapons testing and evaluation, clinical surveillance, operations, and research) is not coordinated or standardized, elevating the challenges in locating vital information.
3. Current blast models are isolated, lack comparability, and have limited automation.
4. Validated protocols or common data elements are often not used.

These significant gaps notwithstanding, the team broadened its efforts to include the development of a capability for the longitudinal examination and derivation of weapons-based effects (existing and emergent) on Service members' brain health and performance. Accomplishments included data repository development, artificial intelligence (unsupervised and supervised learning), and continued improvements to the FAST-CT algorithm to recognize and process blast signatures from heavy weapon systems.

Future Plans

The team plans to continue documenting recommendations for DOD long-term storage of blast data to support DOD communities such as researchers, materiel development, and test and evaluation. Performers plan to deliver an automated methodology for generating individualized computational models supporting finite element analysis from medical imaging data (such as computed tomography or magnetic resonance imaging scans). Researchers could use the methodology to examine individual factors affecting brain injury risk and enhanced capabilities for blast data analysis.

LOI 5: Health and Performance

The OPR is the Traumatic Brain Injury Center of Excellence (TBICoE). It is evaluating health and performance outcomes of blast pressure exposure by leveraging human performance optimization programs and existing clinical and research data. The team is evaluating the acute, sub-acute, and chronic health and performance outcomes of Service members exposed to repetitive, low-level, sub-concussive blast pressure, emphasizing data gleaned from wearable sensors.

The team leveraged existing research efforts throughout the DOD and identified 26 relevant completed and ongoing studies to build a portfolio. This portfolio utilizes both epidemiological analyses and prospective data collection to identify and characterize adverse brain health and performance outcomes related to acute and chronic low-level blast overpressure exposure, with the following objectives:

- Evaluate health and performance outcomes of blast pressure exposure focused on Service member brain health.
- Leverage human performance optimization programs and existing clinical and research data.

Accomplishments

The LOI 5 portfolio will increase the understanding of blast pressure effects on brain health. Listed below are recent key published findings from the study portfolio.

- Neurocognitive assessments have revealed that measures of reaction time are altered by low level blast (LLB) exposure.
- Changes in other neurocognitive domains have not been consistently observed across studies.
- Most common symptom complaints are focused on headaches, fatigue, and sensory related symptoms, notably tinnitus.
- Greater lifetime LLB exposure is associated with a greater risk for diagnoses of tinnitus, TBI, and post-concussive symptoms.
- There are no consistent findings on molecular biomarkers and/or neuroimaging correlates that can be used to track the effects of LLB exposure.

Findings from these studies have facilitated the proposal of a blast overpressure exposure guidance for mitigating brain health hazards to DOD personnel. The report detailing this interim blast overpressure exposure guidance has been briefed to the Deputy Assistant Secretary of Defense for Health Readiness Policy and Oversight and the Deputy Assistant Secretary of Defense for Safety and Occupational Health. Dissemination of this guidance is underway.

Key publications and presentations resulting from work included in the LOI 5 portfolio are summarized below.

1. Streamlining Blast Terminology to Increase Understanding and Comprehension of Blast Across Multi-disciplinary Health-Related Research

After conducting a scoping review, researchers from the Naval Health Research Center and University of Maryland found that the language, terminology, and conceptualization of relevant

constructs in blast exposure research are inconsistent across the literature. They summarized the descriptive conventions currently used within literature when describing blast-related exposures and outcomes. They offer prescriptive conventions on clearly conceptualizing and explicitly defining the relevant constructs of high-level blast (HLB) and low-level blast (LLB) exposure. The authors further articulate how the terminology (such as "acute" or "chronic") should be used when referring to the varying levels of blast exposure and health-related consequences. These universal language-change recommendations and standardizations enhance the understanding of blast exposure across multi-disciplinary backgrounds, strengthen the ease of interpretation and integration of findings across studies, and reduce redundant research to further advance new findings.

This study was supported by the U.S. Army Medical Research and Development Command and was published in Frontiers in Neurology (Belding et al., 2021).

2. Comparing the Negative Effects of High-Level and Low-Level Blast on Animal and Human Health Outcomes

Researchers at the Naval Health Research Center conducted a comprehensive literature review on the damaging effects of blast injury and/or exposure on human and animal health. Blast-related articles published between January 2000 and 2019 were reviewed with specific inclusion and exclusion criteria. The research team identified 3,215 blast-related articles. The animal studies predominantly used shock tubes to induce blast exposure in rats and found that LLB exposure is associated with brain injury. However, there was wide variability in the exposures assessed in training environments with humans, and outcomes evaluated on military and law enforcement personnel in the LLB human studies. The researchers indicated the findings were mixed and therefore the results are inconclusive. While the review describes the adverse effects of LLB on health outcomes, the authors advise future work should consider conducting studies with larger sample sizes, inviting multi-disciplinary collaboration, and standardizing blast exposure terminology and language.

This study was supported by the U.S. Navy Bureau of Medicine and Surgery and was published in the Frontiers in Neurology (Belding et al., 2021).

3. Examining Self-Reported Concussion Symptomology Differences Due to Mechanism of Injury and/or Low-Level Blast Exposure

Researchers from the Naval Health Research Center collected data from 181,423 active-duty Service members deployed between 2003 and 2012 who completed the Post-Deployment Health Assessment. The team then examined the self-reported symptoms of Service members who completed a mild TBI (mTBI) screen and could be classified as a high- or low-risk for LLB exposure (n = 12,013). Symptoms were assessed across four variables: potentially concussive event mechanism (blast vs. impact), probable mTBI (yes vs. no), occupational risk of LLB (high vs. low), and symptom type (neurological vs. musculoskeletal vs. immunological).

Overall, musculoskeletal symptoms were reported the most. However, Service members with probable mTBIs (regardless of the cause of injury) and those with probable blast-related mTBIs reported more neurological symptoms. Those with a high risk of LLB exposure who sustained probable mTBIs also reported a significant increase in neurological symptomology. The findings supported that blast-related mTBIs and impact-related mTBIs may be different, and LLB exposure may increase susceptibility to injury.

This study was funded by the United States Army Medical Research and Development Command under work unit number N1629, and was published in the Journal of Neurotrauma (Belding et al., 2020).

Photo credit: Staff Sgt. Walter Lowell/U.S. Army

4. Measuring the Cumulative Levels of Blast and Risk of Recurrent Occupational Overpressure (ROPE) That Could Predict Probable TBIs

A team of researchers at the Naval Health Research Center studied the effects of high vs. low levels of recurrent occupational overpressure exposure (ROPE) on mTBI after acute, high-level blast exposure. They analyzed active-duty enlisted Service members (n = 12,929) who sustained probable mTBI and who held at least one qualifying exposure. Researchers found blast and ROPE were both independently and jointly correlated with having a potential mTBI. Service members who endured a blast and a high level of ROPE were more likely to sustain a probable mTBI. In addition, Service members who endured a blast and were in high-risk occupations during deployment were more likely to sustain a probable mTBI than those in low-risk occupations. The findings indicated that Service members who experienced blast exposure during deployment and ROPE were likely to sustain a probable mTBI. This implies that ROPE is a risk factor that heightens the susceptibility to mTBI following blast.

This study was supported by the U.S. Army Medical Research and Development Command and was published in Military Medicine (Belding et al., 2020).

5. Comparing the Persistence of Blast- and Impact-Induced Concussion-Like Symptoms Reported Post-Deployment

Researchers at the Naval Health Research Center and TBICoE conducted a retrospective cohort study of active-duty enlisted Service members who deployed between 2008 and 2012, completed the Post-Deployment Health Assessment and Post-Deployment Health Re-Assessment (n=102,075),

experienced a mTBI-inducing event, and completed an mTBI screen (n = 8,106). They examined the persistence of concussion-like symptoms (neurological, musculoskeletal, and immunological) self-reported after deployment, due to probable concussion from an impact-induced injury, LLB or HLB exposure, and specialized occupational risk. Results show HLB-induced mTBIs (vs. impact-induced) were correlated with significantly more neurological symptoms post-deployment. Service members working in LLB-exposed occupations still reported experiencing elevated neurological symptomatology. The findings imply that blast-induced brain injury may be different from impact-induced injuries and that an increased need for screening and treatment for both HLB and LLB exposed patients exists.

This work was supported by the U.S. Army Medical Research and Development Command and published in the Journal of Head Trauma Rehabilitation (Belding et al., 2021).

6. Evaluating the Correlation Between Neurotrauma Biomarker Levels and Concussion-Related Symptoms of Military and Law Enforcement Personnel Exposed to Low-Level Occupational Overpressure

Researchers at Walter Reed Army Institute of Research conducted a retrospective cohort study to evaluate serum levels of neurotrauma biomarkers and their association to self-reported concussion-related symptoms. They collected serum samples and survey data from Service members and law enforcement personnel who have not been diagnosed with a TBI or blast exposure but have prior low-level overpressure exposure. Serum levels of neurotrauma biomarkers (n = 30 randomly sampled from larger cohort) were compared with age-matched controls (n = 30). The results showed increased serum levels among the biomarkers, self-reported ear ringing, memory loss, and difficulty sleeping in the study cohort. The results indicate that low-level overpressure exposure during occupational training may be correlated with elevated serum levels of biomarkers. The relationship between the elevated biomarkers and concussion-like symptoms may inform an increased concentration on military occupational medicine risk management.

This work was supported by the Combat Casualty Care Research Program, the U.S. Army Medical Research and Development Command Military Operational Medicine Research Program (Research Area Directorate III), the Office of the Assistant Secretary of Defense for Health Affairs, and the Research Participation Program at WRAIR. It was published in the JAMA Network Open medical journal (Boutté et al., 2021).

7. Assessing the Long-Term Effects of Blast Exposure on Sensory Organization and Postural Limits of Stability among Military Breachers

To investigate postural instability in experienced breachers, researchers at the Naval Medical Research Center, National Institutes of Health, University of Florida, The Pennsylvania State University, Walter Reed Army Institute of Research, and University of Virginia compared postural and normative data to determine if experienced breachers, with a history of occupational LLB exposure, exhibited postural instability. The authors found the study cohort scored significantly lower on the NeuroCom Sensory Organization Test and experienced slower reaction times and slower sensory movement on the Limits of Stability (LOS) test. These results suggest that while acute effects of blast on sensory orientation disappear, the chronic effects on postural LOS may linger.

This work was supported and sponsored by the Joint Program Committee-5 Development of Exposure Standards to Repeated Blast Exposure program, Office of Naval Research, with supplemental funding from the Cohen Veterans Bioscience, imaging resources from the Center for Neuroscience and Regenerative Medicine, and the Clinical Neurosciences Program of the National Institute of Neurological Disorders and Stroke. It was published in the Journal of Occupational and Environmental Medicine (Haran et al., 2021).

8. Assessing Breaching Occupational Risk on Audiological and Vestibular Performance after Recurrent Blast Exposure

Researchers at the Naval Medical Research Center, Walter Reed Army Institute of Research, National Institutes of Health, Uniformed Services University, DOD Joint Artificial Intelligence Center, and the University of Virginia conducted clinical interviews and evaluated audiological and vestibular performance among experienced breachers. Study participants were divided into cohorts of breachers (military and law enforcement explosives professionals who execute a controlled detonation of explosive charges to force entry) and non-breachers, military and law enforcement personnel who do not perform breaching operations. The researchers concluded self-reported audiological problems (such as hearing loss and ear ringing), irritability, and sensitivity to light or noise are associated with breaching occupations. The breachers cohort reported enduring more combat exposure than the non-breachers. Combat exposure was a risk factor associated with memory loss and concentration difficulties in the study. Vestibular and ocular motor outcomes were similar between breachers and non-breachers. The researchers recommend that future studies control for combat exposure when assessing the chronic effects of recurrent blast exposure.

This work was sponsored by the Joint Program Committee-5 Development of Exposure Standards to Repeated Blast Exposure program, the Intramural Research Programs of the National Institute on Neurological Disorders and Stroke, and the National Institute on Deafness and Other Communication Disorders. This work was published in Frontiers in Neurology (Modica et al., 2020).

9. The Development of a Blast Exposure Estimator to Target Heavy Weapon Systems-Associated Outcomes and Evaluate Adverse Effects

A team of researchers from the Naval Medical Research Center and Walter Reed Army Institute of Research interviewed Service members (n = 984) about their lifelong exposure to blast and behavioral health. For each participant, they determined a generalized blast exposure value (GBEV) using target outcomes associated with heavy arms. The researchers established a threshold of 200,000 GBEV units at which the participants were likely to consistently report more intense symptoms. Therefore, recurrent LLB exposure crossing the threshold of 200,000 GBEV units may result in the ongoing development of blast-related health outcomes and long-term detrimental effects. These findings suggest that long-term repeated exposure to low-intensity blast overpressure can be tracked and may identify those potentially at risk to lasting outcomes.

This work was supported by the Joint Program Committee-5 Development of Exposure Standards to Repeated Blast Exposure program, work unit no. 603115HP.3730.001.A1118. The principal investigator was supported, in part, by an appointment to the Research Participation Program at the Walter Reed Army Institute of Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Army Medical Research and Development Command. This work was published in the Journal of Neurotrauma (Modica et al., 2021).

10. Identifying the Differences in Functional and Structural Neuroimaging in Breaching Professionals

A team of researchers from the University of Virginia, National Institutes of Health, University of Florida, The Pennsylvania State University, Oak Ridge Institute for Science and Education, Uniformed Services University, Walter Reed Army Institute of Research, DOD Joint Artificial Intelligence Center, University of Glasgow, and Naval Medical Research Center collected comprehensive data including neuropsychological assessments, blood biomarkers, and magnetic resonance imaging measures. These data were

Photo credit: Staff Sgt. Ryan Brooks/U.S. Air Force

collected from 20 experienced breachers exposed to blasts throughout their careers and 14 military and law enforcement controls to better understand the relationship between repetitive LLB exposure and behavioral and sensory brain imaging differences. To analyze the data, methodology on the similarity-driven multi-view linear reconstruction (SiMLR) approach (which affords statistical analysis of multi-modal data from a small number of subjects each with a large number of data points) is described. The data indicated significant group effects in the data spanning brain structure, function, and blood biomarkers.

This work was supported and sponsored by the Joint Program Committee-5 Development of Exposure Standards to Repeated Blast Exposure program, Office of Naval Research (ONR), with supplemental funding from the Cohen Veterans Bioscience, imaging resources from the Center for Neuroscience and Regenerative Medicine, and the Clinical Neurosciences Program of the National Institute of Neurological Disorders and Stroke. The complete work is published in the Journal of Neurotrauma (Stone et al., 2020).

11. Assessing the Physiological Outcomes of Chronic Explosive Breaching in U.S. Military Warfighters

A team of researchers from James J. Peters VA Medical Center, Icahn School of Medicine at Mount Sinai, and Walter Reed Army Institute of Research conducted a study involving military breachers that are exposed to a controlled LLB during a three-day explosive breaching course and recorded their physiological outcomes, with tinnitus, memory problems, headaches, and sleep disturbances identified as the most reported symptoms. The authors identified 14 significantly differentially methylated regions within genes associated with cumulative (high to low) blast exposure. The findings support potential molecular signatures associated with chronic exposure and symptoms.

This work was supported by the Veterans Affairs Office of Research and Development, U.S. Army Medical Research and Development Command, Military Operational Medicine Research Program (MOMRP), Office of the Assistant Secretary of Defense for Health Affairs, Combat Casualty Care Research Program, and the Walter Reed Army Institute of Research (WRAIR). This research is published in the Frontiers in Neurology (Wang et al., 2020).

12. Presentations

LOI 5 performers took advantage of multiple opportunities to present their findings during FY21. Of note, leading researchers at Walter Reed Army Institute of Research and Uniformed Services University presented their findings on the health and performance effects of LLB exposure and/or coordinated sessions on blast exposure at multiple conferences. Two of the key conferences that these performers were involved with were the Blast Injury Conference ([Hosted by Imperial College London] July 2021) and the National Neurotrauma Society Annual Symposium (July 2021). These opportunities allowed for the dissemination of data related to LLB exposure to a broad scientific community and fostered discussions that will inform future studies.

Future Plans

The team plans to review and synthesize published and unpublished findings on acute and chronic health and performance outcomes associated with acute and chronic exposures. The synthesis of these data will inform the Capstone Technical Report in FY22 and guide the research field in a more targeted investigation of LLB effects.

LOI 5 FY22 planned briefings:

- An overview of the LOI 5 portfolio and key findings will be briefed at the Joint Army, Navy, NASA, and Air Force meeting in December in a special session focused on the NDAA Section 734 Program and their efforts to characterize health effects related to blast exposure.

- An LOI 5 Work Group Meeting with LOI 5 performers and other subject matter experts will be held to discuss the synthesis of published and unpublished data. The meeting will help identify the most salient health and performance domains and the most sensitive measures within those domains that identify adverse effects from acute and chronic low-level blast exposure; identify existing capability gaps; develop a targeted research strategy with an associated timeline to advance the state of the science in the identified domains and measures of interest and to address the current capability gaps.

- LOI 5 plans to coordinate and present an overview of findings from studies in the LOI 5 portfolio as part of the breakout session titled “NDAA FY18 Sec 734 — The Longitudinal Medical Study on Blast Exposure of Members of the Armed Forces: Program Overview and Updates” at the Military Health System Research Symposium meeting anticipated for late FY22.

Next Steps: Integrating and Communicating Results

The NDAA Section 734 Program continues to leverage existing work and expertise across the various LOIs. The efforts are synergistic and interconnected, resulting in close coordination and collaboration between the medical, scientific, technological, and operational communities. These efforts will inform safety standards, operational techniques, tactics, procedures, and medical policy to maximize force health protection. Additionally, this work will address tracking and documenting blast exposure capabilities.

The continuation of the SARS CoV-2 pandemic slowed progress. Still, as travel restrictions for mission-essential work have been lifted, most efforts have resumed, and the study continues to move forward.

During the next year, the NDAA Section 734 Program will examine the technical findings from across the LOIs’ efforts to develop an integrated view of the work, outcomes, and impacts for communication to senior leaders and stakeholders. The examination and assimilation of efforts will support the demonstration of the work aligned to critical Doctrine, Operations, Training, Materiel, Leadership, Personnel, Facilities, and Policy (DOTMLPF-P) decisions to deliver capabilities optimizing outcomes for the individual Warfighter and the Services.

Reference: FY18 NDAA, Public Law 115-91, Congressional Language Section 734

(a) In general. —The Secretary of Defense shall conduct a longitudinal medical study on blast pressure exposure of members of the Armed Forces during combat and training, including members who train with any high overpressure weapon system, such as anti-tank recoilless rifles or heavy-caliber sniper rifles.

(b) Elements. —The study required under subsection (a) shall—

(1) monitor, record, and analyze data on blast pressure exposure for any member of the Armed Forces who are likely to be exposed to a blast in training or combat.

(2) assess the feasibility and advisability of including blast exposure history as part of the service record of a member, as a blast exposure log, in order to ensure that, if medical issues arise later, the member receives care for any service-connected injuries; and

(3) review the safety precautions surrounding heavy weapons training to account for emerging research on blast exposure and the effects of such exposure on the cognitive performance of members of the Armed Forces.

(c) Reports. —

(1) INTERIM REPORT. —Not later than one year after the date of the enactment of this Act, the Secretary shall submit to the Committees on Armed Services of the Senate and the House of Representatives an interim report on the study methods and action plan for the study under subsection (a).

(2) FINAL REPORT. —Not later than four years after the date the Secretary begins the study under subsection (a), the Secretary shall submit to the Committees on Armed Services of the Senate and the House of Representatives a report on the results of such study.

Reference: FY20 NDAA, Public Law 116-92, Section 742

a) MODIFICATION OF STUDY. —Section 734 of the National Defense Authorization Act for the Fiscal Year 2018 (Public Law 115–91; 131 Stat. 1444) is amended—

Amendments to FY18 NDAA, Public Law 115-91, Sec. 734 are shown in red below

(a) In general. —The Secretary of Defense shall conduct a longitudinal medical study on blast pressure exposure of members of the Armed Forces during combat and training, including members who train with any high overpressure weapon system, such as anti-tank recoilless rifles or heavy-caliber sniper rifles.

(b) Elements. —The study required under subsection (a) shall—

(1) monitor, record, and analyze data on blast pressure exposure for any member of the Armed Forces who are likely to be exposed to a blast in training or combat.

(2) assess the feasibility and advisability of including blast exposure history as part of the service record of a member, as a blast exposure log, in order to ensure that, if medical issues arise later, the member receives care for any service-connected injuries

(3) review the safety precautions surrounding heavy weapons training to account for emerging research on blast exposure and the effects of such exposure on the cognitive performance of members of the Armed Forces.

(4) assess the feasibility and advisability of--

(A) uploading the data gathered from the study into the Defense Occupational and Environment Health Readiness System – Industrial Hygiene (DOEHRS-IH) or similar system.

(B) allowing personnel of the Department of Defense and the Department of Veterans Affairs to have access to such a system; and

(C) ensuring such data is interoperable and can be uploaded into the MHS Genesis electronic health record or successor system of the Department of Defense.

(c) Reports. —

- *(1) INTERIM REPORT. —Not later than one year after the date of the enactment of this Act, the Secretary shall submit to the Committees on Armed Services of the Senate and the House of Representatives an interim report on the study methods and action plan for the study under subsection (a).*
- *(2) ANNUAL STATUS REPORT.—Not later than January 1 of each year during the period beginning on the date of the enactment of the National Defense Authorization Act for Fiscal Year 2020 and ending on the completion of the study under subsection (a), the Secretary shall submit to the Committees on Armed Services of the Senate and the House of Representatives a status report on the study.*
- *(3) FINAL REPORT. —Not later than four years after the date the Secretary begins the study under subsection (a), the Secretary shall submit to the Committees on Armed Services of the Senate and the House of Representatives a report on the results of such study.*

Reference: FY19 NDAA, Public Law 115-232, Section 253

(a) INITIAL REVIEW. —Not later than 180 days after the date of the enactment of this Act, the Secretary of Defense shall review the decibel level exposure, concussive effects exposure, and the frequency of exposure to heavy weapons fire of an individual during training exercises to establish appropriate limitations on such exposures.

(b) ELEMENTS. —The Review required by subsection (a) shall take into account current data and evidence on the cognitive effects of blast exposure and shall include consideration of the following:

- *(1) The impact of exposure over multiple successive days of training.*
- *(2) The impact of multiple types of heavy weapons being fired in close succession.*
- *(3) The feasibility of cumulative annual or lifetime exposure limits.*
- *(4) The minimum safe distance for observers and instructors.*

(c) UPDATED TRAINING GUIDANCE. —Not later than 180 days after the date of the completion of the Review under subsection (a), each Secretary of a military department shall update any relevant training guidance to account for the conclusions of the Review.

(d) UPDATED REVIEW. —

(1) IN GENERAL. —Not later than two years after the initial Review conducted under subsection (a), and not later than two years thereafter, the Secretary of Defense shall conduct an updated review under such subsection, including consideration of the matters set forth under subsection (b), and update training guidance under subsection (c).

(2) CONSIDERATION OF NEW RESEARCH AND EVIDENCE. —
– Each updated Review conducted under paragraph (1) shall take into account new research and evidence that has emerged since the previous Review.

–(e) BRIEFING REQUIRED. —The Secretary of Defense shall brief the Committees on Armed Services of the Senate and the House of Representatives on a summary of the results of the initial Review under subsection (a), each updated Review conducted under subsection (d), and any updates to training guidance and procedures resulting from any such review or updated Review.

Reference: FY20 NDAA, Public Law 116-92, Section 717

SEC. 717. (a) REQUIREMENT.—If a covered incident occurs with respect to a member of the Armed Forces, the Secretary of Defense, in coordination with the Secretaries of the military departments, shall document blast exposure history in the medical record of the member to assist in determining whether a future illness or injury of the member is service-connected and inform future blast exposure risk mitigation efforts of the Department of Defense.

(b) ELEMENTS. —A blast exposure history under subsection (a) shall include, at a minimum, the following:
(1) The date of the exposure.
(2) The duration of the exposure and, if known, the measured blast pressure experienced by the individual during such exposure.
(3) Whether the exposure occurred during combat or training.

(c) REPORT. —Not later than one year after the date of the enactment of this Act, the Secretary of Defense shall submit to the Committees on Armed Services of the Senate and the House of Representatives a report on the types of information included in a blast exposure history under subsection (a).

(d) COVERED INCIDENT DEFINED. —In this section, the term "covered incident" means a concussive event or injury that requires a military acute concussive evaluation by a skilled health care provider.

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Photo credit: NATO

CHAPTER 5:

NATO ENGAGEMENTS

The advancement of blast injury prevention and treatment research relies not only on close collaborations within the DOD and other federal agencies but also on relationships cultivated with other international partners, researchers, clinicians, engineers, and stakeholders. BIRCO participates in and facilitates several collaborative efforts of global scope and interest, attracting the best talent and technology the world has to offer to focus on the protection of Service members both in the deployed environment and in perpetuity at home. These activities include ongoing leadership of North Atlantic Treaty Organization (NATO)-sponsored efforts to pool scientific and technical expertise to direct mitigation strategies for blast injury. Through BIRCO's collaborative international engagements, the United States exchanges knowledge and insights on blast injury research with other nations to improve our Service members' resilience against blast injury.

Explosive weapons remain a significant source of casualties and injuries in NATO operations, with a broad spectrum of blast events including both mounted and dismounted operational scenarios. Recent advances in personal protective equipment (PPE), in-theater medical care, and rapid evacuation are increasing the survivability of blast encounters. Survivors of blast injuries commonly suffer from traumatic brain injury (TBI), visual and auditory system injuries, and extremity injuries resulting in the amputation of the affected limb(s). NATO advances blast injury research through Science and Technology (S&T) activities.

NATO Science and Technology Organization

The Science and Technology Organization (STO) is a NATO subsidiary body established to meet the collective S&T needs of 26 NATO nations and 21 partner nations to counter emerging and evolving security threats. S&T activities consist of 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.

- **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.
- **In-House Delivery**: S&T activities are conducted in a NATO-dedicated executive body, having its own personnel, capabilities, and infrastructure.

Collaboration Support Office Technical Panels

The Collaboration Support Office (CSO) is one of three executive bodies within the STO. The CSO offers executive and administrative support for NATO and partner nation activities (such as defining, conducting, and promoting cooperative research and information exchange) within the framework of NATO's collaborative business model. The CSO consists of six Technical Panels and one Group (Table 5-1) focusing on different S&T areas. Technical Panels and Groups are the entities that drive state-of-the-art science and technology collaborations. These technical panels and groups consist of technical team members (TTMs) that

TABLE 5-1: Six CSO Technical Panels and One Group

Collaboration Support Office	
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

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

are widely recognized scientists, engineers, and information specialists from NATO and partner nations that drive the collaborative S&T activities. The TTMs conduct specific research activities of defined duration and format such as task groups, workshops, symposia, specialists' meetings, lecture series, and technical courses.

Human Factors and Medicine Panel

The mission of the Human Factors and Medicine (HFM) Panel, one of the six CSO Technical Panels, is to provide the scientific and technological base for optimizing health, human protection, well-being, and performance of Service members in operational environments with consideration of affordability. This mission is accomplished by information exchange, collaborative experiments, and shared field trials; it also involves understanding and ensuring the physical, psychological, and cognitive compatibility among military personnel, technological systems, missions, and environments.

History of BIRCO's Involvement in NATO Activities

NATO HFM Panel activities seek to develop a greater understanding of the mechanisms of blast injury and to translate scientific discoveries into prevention, mitigation, and treatment measures. Since April 2008, BIRCO has carried out the role of the executive agent (EA) to foster collaboration within and outside the DOD by participating in these activities, which allow BIRCO to facilitate multi-disciplinary blast injury research across the international community. Since 2011, BIRCO has chaired or co-chaired the NATO HFM activities listed in Table 5-2.

HFM-207 Symposium: A Survey of Blast Injury across the Full Landscape of Military Service

From October 3–5, 2011, BIRCO and the Defence Research and Development Canada – Suffield Research Centre co-chaired the NATO HFM-207 Research Symposium, "A Survey of Blast Injury Across the Full Landscape of Military Science," which was organized by the NATO HFM Panel. The symposium served as an initial assessment of the state of the science for understanding blast injury and highlighted the need for continued cooperation among NATO nations regarding research on blast exposure. The symposium revealed the importance of a systematic approach to understanding blast injuries, much like the well-established approach used to solve the classical toxicology problem where the etiology of the injury requires an understanding of the doses (blast dose), mechanism of delivery of the dosage, and dose-response endpoints. Also recognized was the pressing need for a multi-disciplinary approach to addressing non-penetrating blast injuries to the brain that result in a host of symptoms with vague etiology.

TABLE 5-2: NATO HFM Activities Related to Blast Injury 2011-2025

NATO HFM Activities that BIRCO Chaired or Co-Chaired	Year
HFM-207 Research Symposium: A Survey of Blast Injury Across the Full Landscape of Military Science	2011
HFM-234 Research Task Group (RTG): Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards	2013-2016
HFM-270 (RTG): Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-Related Threats	2016-2019
HFM-341 (RTG): Validation of Modeling and Simulation Methodologies for Human Lethality, Injury, and Impairment from Blast-Related Threats	2021-2025
HFM ET-192: Blast Exposure Monitoring in Military Training and Operations	2021-2023

The symposium brought together researchers from multiple disciplines to provide the groundwork to advance an understanding across the spectrum of blast injury. **The HFM-207 Research Symposium focused on ways to achieve the following:**

- Increase the understanding of blast injury in military operations
- Explore and describe the range of blast injuries seen in current NATO operations
- Delineate some of the medical treatment strategies employed by NATO medical personnel

The HFM-207 Research Symposium resulted in two recommendations:

- Establish a recurring technical exchange discussion forum on blast injury and its mitigation
- Develop and implement a Technical Activity Proposal (TAP) exploring "The Toxicology of Blast Injury" that focuses on models and methodologies to advance translational research

The HFM-207 Research Symposium identified a key need for leveraging computational models to describe the blast threat, the interaction of the threat with the protection system, the interaction of the protection system with the human, the ultimate blast loading on the human (or blast dose), and the spectrum of human responses (from impairment to lethality).

Following the recommendations from the HFM-207 Research Symposium, BIRCO submitted the "Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards" TAP. The NATO STO's approval of the TAP in October 2012 established the HFM-234 (RTG).

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

BIRCO chaired the NATO HFM-234 (RTG), which was established to develop tools and guidelines for conducting focused, multi-disciplinary research that would lead to an understanding of the mechanisms of blast injuries necessary for developing effective prevention, mitigation, and treatment strategies. The team's efforts were guided by the approach used to solve the classical toxicology problem.

The NATO HFM-234 (RTG) developed several key products including:

- ***Guidelines for Conducting Epidemiological Studies of Blast Injury*** that provide investigators with an epidemiologic framework and best practices for data collection and identify critical elements of a blast injury epidemiological study (Bieler et al., 2019)
- ***Guidelines for Reproducing Blast Exposures in the Laboratory*** that provide blast injury research laboratories with fundamental characteristics for collection and description of blast pressure waves (Josey et al., 2019)
- ***Guidelines for Using Animal Models in Blast Injury Research*** that both provide a framework for scientifically valid methodological approaches to address the pathological consequences of blast exposures and also assist researchers during all stages of blast trauma animal experiments (Watts et al., 2018)
- ***Comprehensive Dictionary of Blast Injury Terms*** that provides a common vocabulary to improve information sharing and facilitate collaboration across diverse research communities and disciplines
- ***Environmental Toxicology of Blast Exposures: Injury Metrics, Modelling, Methods and Standards***, a final technical report on HFM-234 (RTG) activities (Leggieri et al., 2019)

Photo credit: NATO

To build upon progress made by the HFM-207 Research Symposium and HFM-234 (RTG), which highlighted requirements for biomedically valid computational models and simulation of blast injury that incorporate biomechanical and physiological responses, BIRCO proposed a new RTG leveraging previous, ongoing, and planned blast injury biomedical research and computational modeling efforts among the participating nations. The HFM RTG proposal was approved by the NATO STO in late 2015 and resulted in the establishment of the new NATO HFM-270 (RTG) on "Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-Related Threats."

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

BIRCO chaired the NATO HFM-270 (RTG) that included seven NATO nations (Canada, France, Germany, the Netherlands, Turkey, the United Kingdom, and the United States), two partner nations (Israel and Sweden), and the non-NATO affiliated South Africa. The HFM-270 (RTG) aimed to develop a multi-scale, multi-resolution, computational framework consisting of component models capable of providing threat-to-outcome modeling and simulation (M&S) of human lethality, injury, impairment, and long-term health effects across the spectrum of blast-related threats and threat environments. These predictions would then inform the development of PPE, injury diagnostics, combat casualty care techniques, and rehabilitation tools by enabling the rapid development and testing of novel blast protection concepts in a virtual environment. This capability could accelerate the delivery of effective blast protective equipment to Service members by dramatically reducing the time and cost required to develop, build, and live-fire test prototype blast injury protection systems.

The HFM-270 (RTG)'s three-year effort produced the Framework that lays the groundwork for developing a comprehensive, threat-to-outcome computational modeling capability capable of supporting an agile and streamlined approach to designing, testing, and fielding blast protection equipment for NATO Service members. The Framework provides a comprehensive and logical structure within which individual models can interact to produce the desired threat-to-outcome modeling capability. It is unique because it reflects the knowledge, perspectives, and needs of the diverse communities and disciplines represented by the HFM-270 (RTG) TTMs.

The HFM-270 (RTG) developed four key products:

- An extensive literature review that identifies relevant, existing computational models that may be appropriate for inclusion in the framework
- A comprehensive list of modeling gaps that can inform future investments in computational model research and development
- A robust repository of information about existing models and modeling capabilities that will be available to NATO and NATO partner nations
- A comprehensive dictionary of M&S terms that enhances communication and collaboration among the diverse communities and disciplines needed to sustain and advance the modeling capabilities enabled by the Framework

In FY20 and FY21, the NATO HFM-270 (RTG) TTMs prepared the final NATO technical report that includes an extensive literature review of existing computational models, findings, a robust repository of information on existing modeling capabilities, and a comprehensive dictionary of modeling and

Photo credit: NATO

simulation terms. The TTMs also identified a critical need for consistent and adequate level of validation measures to substantiate the capabilities of computational models and to establish a direct comparison of model accuracies for the same experimental data sets.

BIRCO, in collaboration with the HFM-270 (RTG) TTMs, submitted a TAP to address the HFM-270 recommendations and to develop a NATO activity devoted to validating M&S methodologies. NATO STO approved the TAP in 2021 and established the new HFM-341 (RTG) on "Validation of Modeling and Simulation Methodologies for Human Lethality, Injury and Impairment from Blast-Related Threats".

Ongoing Activities

NATO HFM-341 (RTG): Validation of Modeling and Simulation Methodologies for Human Lethality, Injury, and Impairment from Blast-Related Threats

BIRCO chairs this RTG that includes five NATO nations (Canada, Germany, Italy, Norway, and the United States), one partner nation (Japan), and the non-NATO affiliated South Africa. (See Figure 5-1) The concept of using computational modeling in HFM-207, and injury criteria and representation in HFM-234 formed the foundation to create a framework for blast injury computational modeling simulation in HFM-270 (RTG). A key need identified in the HFM-270 (RTG) was a consistent and adequate level of validation, as well as

FIGURE 5-1: NATO HFM-341 Technical Team Members

NATO HFM-341 TECHNICAL TEAM MEMBERS

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SOUTH AFRICA

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researchers using consistent validation criteria and measures to substantiate the capabilities of their computational models. Thus, although HFM-270 (RTG) found a number of credible models to simulate the blast effects on the Warfighter, many of these with their own model validation approaches, it was not possible to establish a direct comparison of model accuracies for the same experimental data sets.

NATO HFM-341 (RTG) aims to develop standardized methodologies and criteria to validate computational models and simulation approaches established in the HFM-270 (RTG) for the entire spectrum of blast-related injuries to mounted and dismounted personnel and what is required to prevent injury, impairment, and lethality prediction framework. The RTG will utilize the latest scientific, experimental, and combat theater data to include, but not limited to, prediction of performance of protective equipment in blast explosions, as well as combat scenario predictions. The outcome will be an approach and criteria to validate component computational models and simulation techniques.

Taking a multi-disciplinary scientific approach, the HFM-341 (RTG) plans to leverage previous, ongoing, and planned blast injury biomedical research and computational modeling efforts among the participating nations. It will lead to validation of a framework for translating scientific information into the capability to model human lethality, injury, and impairment across the spectrum of blast-related threats. The validation process will pull together existing scientific data and computational models to identify the gaps in understanding injury mechanisms from both mounted and dismounted blasts. In parallel with development of blast injury mechanisms, the validation strategy will also support other efforts aimed at creating and evaluating effective blast injury protection systems. Creating the validation strategies, existing component models, and validation techniques — along with identifying gaps that require additional research to comprehensively understand blast injury mechanisms and the requirements to prevent injury, lethality, and impairment — may reduce the time required to develop and field effective blast injury protection systems.

On July 28, 2021, the NATO HFM-341 (RTG) TTMs convened to participate in a virtual pre-kickoff meeting of eighteen representatives from Canada, South Africa, and the United States. The purpose of this meeting was to initiate collaboration between the TTMs by facilitating introductions for the participating members. During the meeting, representatives introduced themselves by providing a brief description of their responsibilities, areas of expertise, and organizations. These introductions enabled the team members to consider collaborative opportunities with other complementary research efforts.

The Chair of the NATO HFM-341 (RTG) provided a level-setting brief for all TTMs, reviewing the purpose and findings from the NATO HFM-270 (RTG) that led to the creation of the NATO HFM-341 (RTG). The Chair provided an overview of the NATO HFM-270 (RTG) including a brief overview of the purpose, objectives, deliverables, key findings, and the 22 appointed TTMs from 10 Nations. The group reviewed the fundamentals of blast physics, categories of blast injuries established by the DOD, the threat-to-outcome model generated by the HFM-270 (RTG), an introduction of the framework for connecting these computational models, the knowledge gaps identified, and recommendations for follow-on activities. The Chair introduced the TTMs to the NATO HFM-341 (RTG) objective, goals, and deliverables. The TTMs discussed the possible topics for the NATO HFM-341 (RTG) Kickoff Meeting, the logistics of hosting an in-person meeting in France given COVID-19 restrictions, and a plan for the next virtual pre-kickoff meeting.

Photo credit: NATO

NATO HFM Exploratory Team (ET)-192 Blast Exposure Monitoring in Military Training and Operations

BIRCO and the U.S. Army Military Operational Medicine Research Program (MOMRP) co-chaired the newly formed NATO HFM Exploratory Team-192, "Blast Exposure Monitoring in Military Training and Operations." Mild traumatic brain injury (mTBI) is a risk for military personnel due to repeated low-level and/or high-intensity blast exposures from sources such as shoulder-fired weapons and improvised explosive devices. Military personnel exposed to blast in training and combat do not have an objectively measured record of blast exposures. Further, there are no reliable biologic or performance markers of effects from these exposures. Canada, the United States, and other nations are pursuing blast exposure monitoring capabilities and/or funding research to better characterize the amount and frequency of blast exposures during training and combat and their effects on military brain health and operational performance.

The mission of the USAMRDC Military Operational Medicine Research Program (MOMRP) is to develop effective biomedical countermeasures against operational stressors and to prevent physical and psychological injuries during training and operations to maximize health, readiness, and performance of Service members and their families. HFM-ET-192's objective is to understand Service members' occupational health hazards resulting from repetitive use of weapon systems and explosives during a military career. The secondary objective is to recommend a need for further exploration of strategies to prevent and mitigate unnecessary exposures and sustain Service members' brain health and performance.

Four key tasks for NATO HFM ET-192:

- Increase understanding of health hazards from extreme environmental exposures resulting from repetitive use of weapon systems and explosives
- Identify health hazards from weapon systems and explosive charges during military operations
- Explore and describe the range of health hazards resulting from repetitive use of weapon systems in current NATO operations
- Delineate some of the medical and/or personnel protection strategies for prevention, mitigation, and treatment of injuries

In FY21, NATO HFM ET-192 TTMs from Canada, South Africa, Sweden, the Netherlands, and the United States held a pre-kickoff meeting. The purpose of the May 26 meeting was to provide the TTMs with an opportunity to introduce themselves to the team, understand the general team member requirements, and discuss and finalize plans for hosting the kickoff meeting at the STO in Paris, France. During this meeting, the team leads described the short- and long-term health hazards resulting from blast exposures in military operational environments such as training or combat and established standards for monitoring, eliminating, and/or controlling the health hazards inherent in weapon platforms and munitions during training and combat.

Way Forward

Over the next fiscal year, BIRCO will actively engage in and leverage partnerships within NATO. Building upon research and expertise from previous NATO activities, BIRCO will foster multidisciplinary collaboration across the international community to advance research on blast injury to improve Service members' health and preparedness for the future fight. In FY22, BIRCO will coordinate the NATO HFM-270 (RTG) efforts to submit the final report to the NATO Collaboration Support Office. BIRCO will continue to chair the NATO HFM-341 (RTG) and prepare for the in-person kickoff meeting in Paris, France in June 2022 where the TTMs will develop the program of work for the validation of computational mathematical models. To meet the needs of the Warfighter, BIRCO will continue to engage with NATO and international partners to promote initiatives and advance research across the spectrum of blast injuries.

Photo credit: NATO

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Photo credit: SSgt Eric Harris/U.S. Air Force

CHAPTER 6:

JOINT TRAUMA ANALYSIS AND PREVENTION OF INJURY IN COMBAT (JTAPIC)

Invited chapter contributed by JTAPIC

Operation Enduring Freedom, Operation Iraqi Freedom, and their successor operations exposed the U.S. Armed Forces to combat in novel environments against an unfamiliar enemy, whose rapidly evolving methods of attack required substantial changes in U.S. vehicles, equipment, and tactics on a timescale much shorter than required for traditional research, development, and acquisition processes. In response, the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) program was established at the U.S. Army Medical Research and Development Command (USAMRDC) in July 2006 to assist in fulfilling portions of the Executive Agent responsibilities under Department of Defense Directive (DODD) 6025.21E, *Medical Research for Prevention, Mitigation and Treatment of Blast Injuries*. (See Appendix C: DODD 6025.21E.)

MISSION

Inform solutions that prevent or mitigate injury during the full range of military operations, by collaborative collection, integration, analysis, and storage of data from operations, intelligence, materiel, and medical sources.

Prior to the establishment of the JTAPIC program, military organizations focused on improving Service member survivability individually rather than collaboratively. The medical community focused on battlefield medicine and increasing Service member survivability by using the best treatment modalities available. Meanwhile, however, few personal protective equipment (PPE) articles were returned for analysis from killed in action (KIA) or wounded in action (WIA) events, so PPE developers could only focus on performance specifications and process improvements under testing conditions. On the rare occasions an article was returned, analysts lacked full knowledge of the operational context — what happened to the Service member and what they were doing at the time of injury — or the injuries sustained. When vehicle improvements were fielded in Operation Iraqi Freedom, for example, no formal process provided developers with relevant contextualized medical information on combat injuries that would help them understand how well the vehicles protected the occupants. Likewise, the medical community lacked a formal process for providing medical injury data associated with combat operations to non-medical users, such as combatant commanders, materiel developers, and requirements developers.

JTAPIC receives requests to perform analyses on theater combat-related events to improve the survivability of Service members and vehicle platforms during combat. The integrated analysis that occurs within the JTAPIC partnership provides actionable decision support to inform solutions across the doctrine, organization, training, materiel, leadership and education, personnel, facilities, and policy (DOTMLPF-P) domains that will prevent or mitigate traumatic injuries during all military operations, including combat.

Although the military focus may change from primarily ground wars to full-spectrum or multi-domain operations, the JTAPIC methodology for the development of rapid, holistic evaluations of casualty-causing combat events across disciplines will prove advantageous to address complex operational challenges in a variety of environments. JTAPIC is a non-materiel enduring capability via the Army G3/5/7, through the Army Requirements Oversight Council (AROC) and the U.S. Army Training and Doctrine Command Capabilities Development for Rapid Transition process. JTAPIC consists of 11 partner organizations overseen by the JTAPIC Program Management Office (PMO).

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

JTAPIC Partners

To streamline and enhance joint service information sharing and collaboration for the analysis and prevention of injuries in combat, JTAPIC functions as a joint "matrix" partnership (Table 6-1).

JTAPIC funds medical, materiel, operations, and intelligence subject matter experts embedded in 11 separate, geographically dispersed partner organizations (Figure 6-1).

Over half (64 percent) of JTAPIC partner organizations are non-medical and 54 percent are non-Army. The JTAPIC PMO manages and coordinates their support and service to the JTAPIC mission.

Additionally, as JTAPIC expands, potential partners both from the DOD and other civilian government agencies are under consideration. The Engineer Research and Development Center (ERDC), which develops and maintains the contemporary JTAPIC Information and Collaboration System (JINCS), and the U.S. Department of Transportation (DOT) John A. Volpe National Transportation Systems Center (Volpe Center), which conduct similar holistic analyses, participate and collaborate with JTAPIC with the intent to become formal partners.

TABLE 6-1: JTAPIC partner organizations and their associated charter responsibilities

Partner Organizations	Unique Responsibilities
U.S. Army Aeromedical Research Laboratory	Provide analysis of aircraft and vehicle injury patterns
Combat Incident Analysis Team (Army)	Collect dismounted operations and intelligence incident data; provide subject matter expertise and analysis
National Ground Intelligence Center (Army)	Collect mounted operations and intelligence incident data; provide forensic vehicle analysis, information management support and services, subject matter expertise, and analysis
Marine Corps Combat Capability Development Command Operations Analysis Directorate	Provide Marine Corps-related operations research analysis and subject matter expertise
Marine Corps Intelligence Agency	Provide Marine Corps-related intelligence analysis and subject matter expertise
Armed Forces Medical Examiner System	Collect KIA injury data; provide KIA injury coding, subject matter expertise, and analysis
Naval Health Research Center	Collect WIA injury data; provide WIA injury coding, subject matter expertise, and analysis
Joint Trauma System	Provide WIA traumatic injury subject matter expertise and analysis
U.S. Army Combat Capability Development Command (DEVCOM) – Data & Analysis Center	Provide forensic evidence (e.g., ballistics, fragments, other metals) analysis, experimentation support and services, comparative analysis between live-fire tests and operational events, survivability and lethality modeling and simulation support and services, information management support and services, subject matter expertise, and analysis
Project Manager, Soldier Survivability, Program Executive Office Soldier (Army)	Collect damaged personal protective equipment (PPE); provide PPE analysis and subject matter expertise
Product Manager, Infantry Combat Equipment (Marine Corps)	Collect damaged Marine Corps PPE; provide PPE analysis and subject matter expertise

FIGURE 6-1: JTAPIC Partner Organizations

Analysis Process Overview

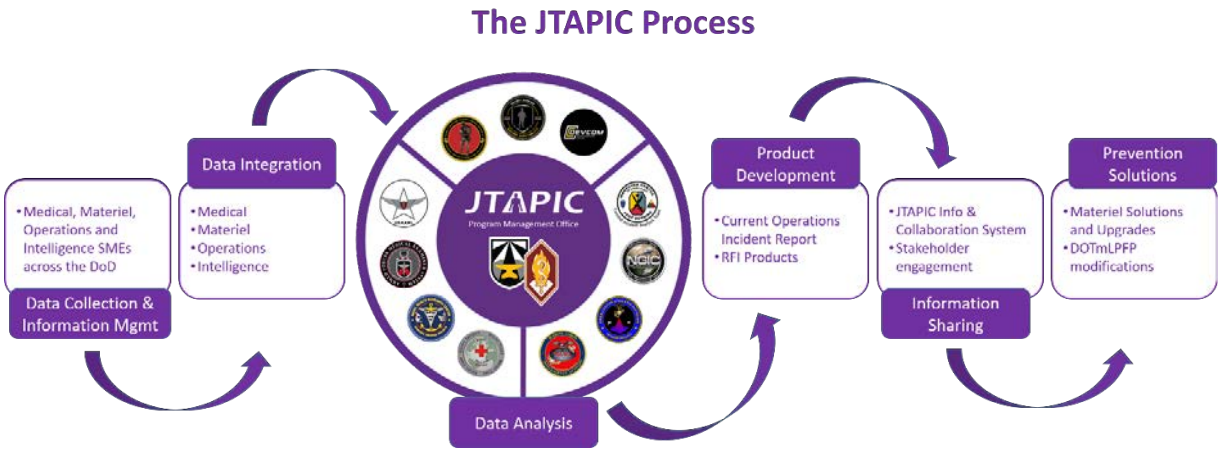
As shown in Figure 6-2, JTAPIC's Operational Concept is to provide actionable analysis of medical, intelligence, operational, and materiel information in order to improve the DOD's understanding of Service members' vulnerabilities to threats and to enable the development of tactics, techniques, and procedures (TTP) and materiel solutions that will prevent or mitigate traumatic injuries.

JTAPIC uses a methodology refined over the past decade and a half incorporating lessons learned and best practices to facilitate efficient multi-disciplinary synergy (Figure 6-3).

After a casualty-producing event, PPE, ballistic fragmentation evidence, threat assessments, and battle damage assessment of vehicular equipment are collected along with operational data. Casualty identification occurs concurrently through medical and operational reporting channels. To analyze a combat event, JTAPIC gathers information from disparate sources of varying classification levels and access points to link cause (incident operational data and analysis), effect (injury and combat casualty care data and analysis), and mitigation (materiel performance data and forensic equipment analysis) factors. Critical capability gaps that JTAPIC has been at the forefront to address

FIGURE 6-2: JTAPIC Operational Concept

FIGURE 6-3: The JTAPIC Analysis Process



include: combat data collection methodology and standardization; in-country materiel recovery and return to the continental United States for analysis; data sharing across Service components and agencies; integration of cross-domain data; and improving timeliness and responsiveness to requests for comprehensive analyses.

The Program Manager Soldier Survivability (PM SSV), Program Manager Infantry Combat Equipment, the Armed Forces Medical Examiner System (AFMES), and U.S. Army Combat Capability Development Command Data and Analysis Center (CCDC DAC) work together on the collection, identification, and analysis of damaged PPE from WIA Service members as well as material fragments removed during post-mortem examination from Service members who were either KIA or died of their wounds. PPE returned from theater are analyzed for damage and performance while the retrieved fragment material properties are characterized (Figure 6-4). Fragment analysis data provides clues to the threat weapons involved in an incident, and modeling provides kinetic energy data useful to PPE and armor developers.

Detailed forensic crosswalks of combat incidents link key information from disparate sources related to a specific combat event. The JTAPIC Combat Incident Analysis Team; the National Ground Intelligence Center, Combat Incident Analysis Division; the Marine Corps Intelligence Agency; and the Marine Corps Combat Development Command/Operations Analysis Directorate provide operations and intelligence data surrounding the incident. AFMES provides information on KIA Service members and the Naval Health Research Center (NHRC), Joint Trauma System (JTS), the JTAPIC PMO Medical Operations Cell (MOC), and U.S. Army Aeromedical Research Laboratory coordinate information on WIA Service members. The CCDC DAC provides analysis on any fragments collected from the incident and models the event, and PEO Soldier/PM SSV analyzes the PPE involved in the incident. A multi-community analysis of each incident provides the “so what” message. JTAPIC customers use these analysis products to guide survivability models and analyses, to support vehicle and equipment development, to inform milestone acquisition decisions, and to characterize injuries typical of a given combat scenario. Specific processes for event types, materiel, personnel, and the dissemination and analysis of data are standardized for efficient management of customer requests.

FIGURE 6-4: Damaged Materiel Analysis

U.S. Army Chief Warrant Officer Sammy Rodriguez, 2nd Battalion, 503rd Infantry Regiment assesses a damaged vehicle to determine how to best recover it to a forward operating base in the Kunar province. None of the vehicle's occupants were injured in the incident.

The protective plate insert inside the 40-pound body armor vest was strong enough to stop a sharp, foot-long piece of metal after the suicide bomber detonated near a Marines outpost.

Current Operations Incident Reporting

JTAPIC analyzes casualty-causing combat events across all Combatant Commands (CCMD) and, when indicated, produces a corresponding Current Operations Incident Report (COIR). COIRs are detailed operational and injury reports of casualty-causing combat incidents, primarily from Special Operations Forces (SOF) in recent years. This effort is coordinated by the JTAPIC PMO and led by the Combat Incident Analysis Team, with contributions from the JTAPIC PMO MOC, NHRC, AFMES, and other partner subject matter experts as appropriate to examine the incident.

As a result of unit-level Special Forces Group requests for analysis, JTAPIC COIRs have been featured in the Special Operations Combat Medic Skills and Sustainment Course and its recertification pathways to provide insight into recent enemy TTPs in relevant geographic areas.

COIRs support unit-level TTPs and course-of-action development, steer training scenarios during unit pre-mission training cycles, and drive requirements.

COIRs serve as a vital piece of the JTAPIC apparatus. These thought-provoking and detailed vignettes have led to requests for information, identified trends, verified information for formal investigations, and populated the JTAPIC database in JINCS. In fiscal year (FY) 2021, JTAPIC analyzed 44 combat incidents involving 85 individuals and 180 injuries and exposures. In response to signals from stakeholders in the mild traumatic brain injury (mTBI) community, FY21 saw the first inclusion of exposures to blast without diagnosed injuries in each COIR report. There were two case studies for sentinel events in FY21.

Photo credit: Staff Sgt. Angelita Lawrence/U.S. Air Force

COIR Spotlight

JTAPIC completed a COIR for the Hamid Karzai International Airport (HKIA) person-borne improvised explosive device (PBIED) attack in August 2021. JTAPIC Partners leveraged their capabilities to provide a thorough, multi-disciplinary analysis of the event, from using computed tomography (DAC) to evaluation of damaged PPE provided by PM SSv and PM ICE, conducting enhanced threat assessments (NGIC/CIAD), and investigating detailed operation timelines and posture analyses (CIAT), multiple medical partners (PMO MOC/AFMES/NHRC) collaborated on injury analysis to thoroughly examine this event from initial contact to clearance. This and other high profile events often have a requirement for an unclassified version. JTAPIC experts are able to transition information so that it is available for widest dissemination in accordance with law, policy, and security classification. Since the event, JTAPIC has received damaged materiel from SMs WIA at HKIA, a first for JTAPIC, and will be updating this product as the analysis effort is completed. The current version of this product is available for viewing and download from JINCS at https://jincs.army.mil/Index?returnUrl=/HomePage.

JTAPIC Request for Information Process

The JTAPIC request for information (RFI) process ensures the broad dissemination and communication of the of the data and analysis products developed by the JTAPIC Partnership as broadly as possible in accordance with DODD 8320.2, *Information Sharing in a Net-Centric DOD*.

The JTAPIC RFI process results in analysis products that fill intelligence gaps and aid in the completion of combat or accident event analyses. These products often contribute to materiel or non-materiel solution modifications and improve overall understanding of vulnerabilities to threats. JTAPIC products also enable the development of improved materiel solutions, PPE, vehicular equipment, and TTPs, which in turn ultimately help develop better ways to prevent and mitigate injuries to Service members. In the future, as JTAPIC transitions to the Defense Health Agency (DHA), JTAPIC intends to make its products more accessible to other agencies in order to strengthen decision support for injury prevention.

DOD personnel with a Common Access Card (CAC) can access JINCS, live as of April 2021, at https://jincs.army.mil/Index?returnUrl=/HomePage to submit an RFI, query the JTAPIC dataset, or view and download completed analysis products.

Requests for Information

JTAPIC responded to 21 RFIs from DOD stakeholders in FY21. At the time of this writing, there are 12 RFIs are in process for FY22. Some of the many DOD/government organizations that JTAPIC has answered RFIs from, completed taskers for, or made significant contribution to in FY21 for prevention-of-injury solutions include the Aviation Shoot Down Assessment Team, Combat Capabilities Development Command Soldier Center, the USAMRDC Commanding General, U.S. Special Operations Command (USSOCOM) J-1, JTS J-3, JTS Director, 75th Ranger Regiment Surgeon, U.S. Army Special Operations Command Surgeon, Next Generation Combat Vehicle Cross Functional Team, Program Manager Joint Light Tactical Vehicle, the Warrior Injury Assessment Manikin (WIAMan) PMO, Army Futures Command (AFC), CCDC DAC, USSOCOM J/5-9, Naval Special Warfare Command, USSOCOM Surgeon, the House Armed Services Committee, the Senate Armed Services Committee, Congressional Representatives, and the DOD Inspector General. JTAPIC projects are specifically requested by the named organization and tailored to provide custom decision support for injury prevention/risk mitigation efforts in progress or in development. JTAPIC continues to serve many repeat customers. The entire list of JTAPIC requests and subsequent products can be viewed in JINCS at https://jincs.army.mil/Index?returnUrl=/HomePage and additional accomplishments are captured in Chapter 7.

RFI Spotlights

In FY21, JTAPIC updated the “Distance and Cover” Push Product on the January 2020 Sentinel surface-to-surface missile attack in Al Asad, Iraq, which generated several inquiries on the event from various Stakeholders. This product identified approximately 460 casualties, abstracted injuries and exposures, recorded estimated distances from blasts, and categorized type of cover and other collateral data from medical records and operational reports. Classified analyses of distance and cover in the attack were synchronized with the Joint Technical Coordinating Group for Munitions Effectiveness (JTCG-ME) analysis, prompting an RFI to interview Service members evacuated from theater following the attack. Eight evacuated Service members were interviewed as part of JTAPIC’s Wounded Warrior Debrief Program; they provided detailed operations viewpoints, filled knowledge gaps, and shed light on readiness and TTPs. JTAPIC provided this information to DOD Stakeholders considering performance improvement and the ERDC for modeling of bunker overpressure to make conclusions about safe stand-off distance. The cumulative JTAPIC effort was presented at the JTCG/ME Capabilities & Standardization Technical Interchange in October 2021.

Photo credit: Staff Sgt. Kate Thornton/U.S. Air Force

Photo credit: Pvt. Austin Anyzeski/U.S. Army

JTAPIC Partners analyzed the engagement ranges of U.S. Service member WIA and KIA events and the injuries sustained from direct fire engagements against dismounted personnel from a population including calendar years 2015–2020. This information is further associated with the number of casualties as well as the injuries by body region and severity for any given casualty. U.S. Army Combat Capabilities Development Command (DEVCOM) will use this information to better understand the threats faced by U.S. Service members, aid in the development of PPE and other protective systems, and inform aspects of doctrine, training, and materiel development.

In support to AFC and with the Maneuver Capabilities Development Integration Directorate at Fort Benning, Georgia, JTAPIC submitted six classified analysis products to the Vehicle Protection Suite (VPS) Strategy Study Team. This study, directed by General John Murray, Commanding General of the AFC, supports the development of a risk model that accounts for "catastrophic" damage events. Prior to JTAPIC providing data analysis regarding personnel injuries sustained on current Army platforms (Abrams, Bradley, M113, MATV) by type and event, the study lacked a specific dataset to help delineate those types of incidents. The VPS study team is reviewing planned combat platform protection technologies and supporting the development of a strategy to move from current platform- and operator-centric technologies to more formation-based capabilities.

In addition, JTAPIC answered seven RFIs from the Veterans Benefits Administration to help clarify claims regarding potentially concussive event exposure and mTBI diagnoses during active-duty service. "VBA Requests" provide detailed descriptions of events that have occurred, but lack corroboration from medical records. In addition to the longer-term effects of multiple untreated concussions and exposures, SMs are often unable to gain appropriate compensation and treatment

coverage for military-related disability after their active-duty service. JTAPIC operational reporting, including the potentially concussive event report database, filled the gaps left by a lack of medical records — allowing Veterans to access the benefits they had earned.

Push Products

JTAPIC retains SMEs in the medical, materiel, operations, and intelligence communities who are keenly aware of evolving trends that warrant further investigation. Primarily, JTAPIC responds to RFIs and requests from the larger DOD community; however, if there is evidence to support internal investigation of a particular trend, JTAPIC will develop and disseminate a push product to communities with vested interest in the subject. JTAPIC push products often initiate more formal, detailed requests and have been a cornerstone for materiel and non-materiel mitigating efforts.

Push Product Highlight

StaticSite Security DOTMLPF-P Implications

JTAPIC compiled doctrinal material and data to develop a static site security product. In 2019, 27 of the 168 SOF casualties (16 percent) occurred during Remain Over Day/Remain Over Night (ROD/RON) static site operations. Of note, 25 of the 27 casualties were sustained when friendly forces were unable to identify positive locations of the enemy. In those cases, enemy personnel were able to get within hand grenade range of the friendly forces' static site. The proximity of dead space, ROD/RON placement, and knowledge of the terrain and avenues of approach, as well as intelligence, surveillance, reconnaissance (ISR) long-look taskings, potentially led to the enemy's ability to achieve close proximity to friendly locations before engaging. JTAPIC's product explores materiel solutions like automated unmanned ground sensors as well as doctrinal and tactical considerations to address this operational concern.

Annual Casualty and Operations Rollup

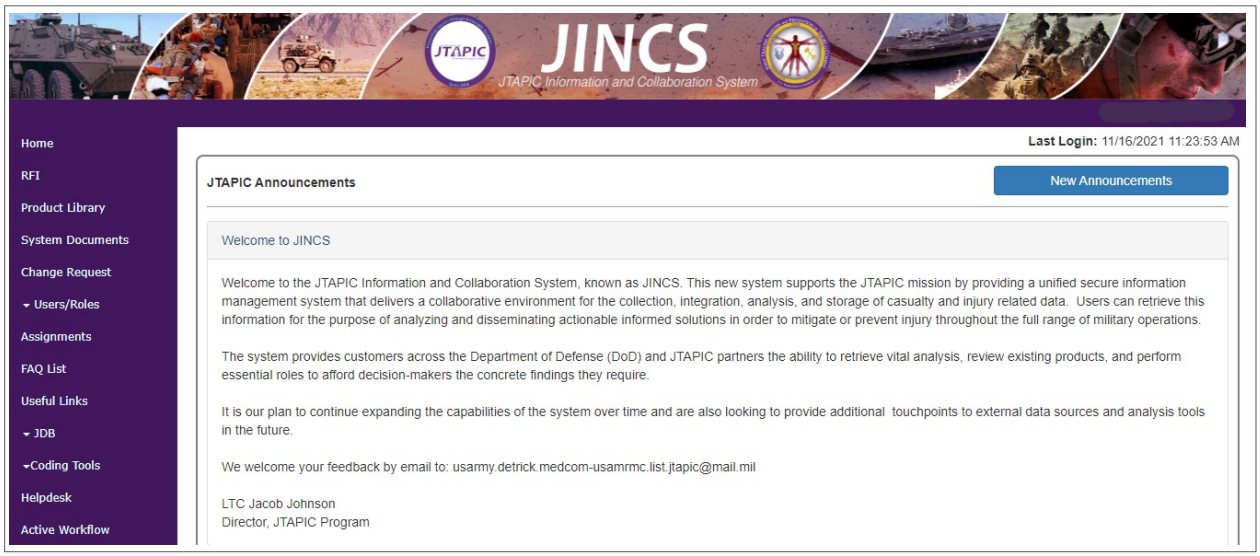
Since 2019, JTAPIC has been publishing an annual analytical operations and casualty report providing military practitioners with a quick reference and baseline situational knowledge and context into circumstances surrounding casualty-producing events and associated medical outcomes. Published in the second quarter of each calendar year, these reports are available in the JINCS Product Library at https://jincs.army.mil/Index?returnUrl=/HomePage as well as in the Lessons Learned Community on MilSuite (https://login.milsuite.mil/), courtesy of the Army Lessons Learned Community. Over the past few years, the reports focused on special operations forces so commands such as USSOCOM, United States Marine Forces Special Operations Command, and United States Army Special Operations Command, can use these reports in conjunction with JTAPIC COIRS and, when needed, quarterly reflections product for education, training, and TTP adjustment prior to deployment.

JTAPIC Information and Collaboration System

Online and available as of April 2021, JINCS supports the JTAPIC mission by providing a unified secure information management system that serves as a collaborative environment for the collection, integration, analysis, and storage of both classified and unclassified information. Users accessing JINCS via their CACs can explore the system for the purpose of analyzing and further disseminating actionable informed solutions that mitigate or prevent injury through a full range of military operations (Figure 6-5).

Designed from the ground up using best practices honed over the past 15 years, JINCS has gathered and integrated multi-disciplinary data. This system will merge previously disparate JTAPIC information systems: the JTAPIC Analysis and Collaboration System, the legacy JTAPIC database, the physical evidence data base, and other datasets maintained

FIGURE 6-5: The JTAPIC Information and Collaboration System (JINCS)



in commercial off-the-shelf data systems, such as the JTAPIC mTBI data repository in Microsoft Access. JINCS encompasses a myriad of modules and applications and provides a collaborative work environment for JTAPIC and its stakeholders. This system stores data, tracks RFIs from submission to completion, houses data relevant to analyses products, includes tools for facilitating analysis in one place, and unifies all JTAPIC information systems. The JTAPIC system will allow customers throughout the DOD to interact with JTAPIC and support its vital work. The JTAPIC system will offer the ability to retrieve vital analyses and perform vital roles in supporting the actionable analysis that gives decision-makers the concrete information they require. In addition, the JTAPIC system will keep the JTAPIC community informed and aware of their services and successes in aiding the DOD.

JTAPIC and DODI 6490.11

mTBI has been regarded as one of the 'invisible and signature injuries' of the wars in Afghanistan and Iraq. The 'drive-on' culture and Service members' reluctance to report an invisible injury have led to significant and consistent underreporting of sustained brain injuries. In 2010, U.S. Central Command (CENTCOM) established a need to document Service members exposed to possible concussive events in theater. This reporting system established an event-based, line-reporting mechanism for exposures to potentially concussive events in an effort to overcome the Service members' reluctance in reporting them. The Blast Exposure and Concussion Incident Report (BECIR) documents an active-duty Service member's exposure to possible concussive events in deployed settings. Those exposed and reported in BECIR undergo mandatory medical evaluation and necessary treatment. The primary purpose is to promote early detection and treatment of mTBI and therefore decrease the risk of long-term symptoms associated with both blast- and non-blast-related mTBI. DOD Instruction (DODI) 6490.11, *Policy Guidance for the Management of mTBI in the Deployed Setting*, supports the system. JTAPIC's responsibility is to report on Combatant Command compliance with the elements in the DODI as well as use the information for the reports to assist DOD TBI stakeholders in creating the analyses as decision support for the evolution of care and treatment of mTBI.

The JTAPIC mTBI Databases house information related to 16,888 Service members identified and evaluated for exposure to potentially concussive events, of whom 2,792 were found to have sustained a concussion. It is widely believed that

event-based reporting of Service members' exposures has led to the identification of concussions that would otherwise have gone unreported. Unreported and delayed treatment of concussions is detrimental to both the Service member and the unit, since Service members may experience poor marksmanship, slower reaction time, decreased concentration, and reduced work quality.

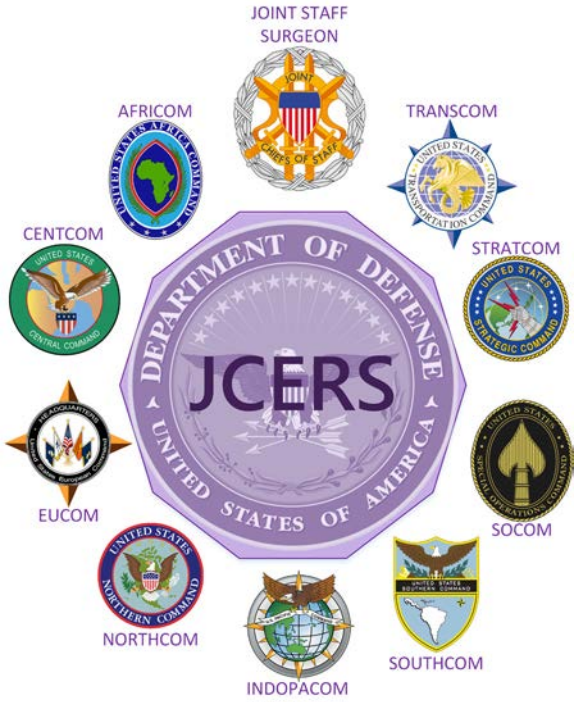
In response to the cessation of reporting after the retrograde and associated drawdown of assets, JTAPIC created a SharePoint site in 2018 accessible on unclassified and classified networks for the reporting of potentially concussive events; it offers flexibility in recording Service members' exposures and mTBI diagnoses.

JTAPIC Concussive Event Reporting System

The JTAPIC Concussive Event Reporting System (JCERS) is a SharePoint-based application (Figure 6-6) intended to facilitate the reporting of potentially concussive events (PCE) from the CCMD level (or its designee) to JTAPIC in accordance with DODI 6490.11. This system allows a user to complete an online form or batch upload PCEs, as in the instance of a mass casualty. JCERS is accessible on unclassified and classified networks. The information provided to JCERS by CCMDs is used to compile data on compliance with DODI 6490.11. The subsequent medical record abstractions that occur for each Service member's record provide decision support for policy, treatment, tracking, and analysis of the complex and substantial burdens mTBI and blast exposures place upon the military.

JCERS is planned for integration into JINCS in early 2022.

FIGURE 6-6: The JTAPIC Concussive Event Reporting System



Novel Applications of JTAPIC Methodologies: New Relationships, New Data, Canine Service Members

JTAPIC maintains a liaison officer position to Headquarters USSOCOM to raise awareness of JTAPIC's efforts. The position helps to facilitate the widest dissemination of JTAPIC analytical products in order to prevent or mitigate SOF casualties, synchronize JTAPIC and SOF efforts to identify vulnerabilities, and increase SOF Service members' lethality and survivability. JTAPIC was designed with the Conventional Forces in mind, but the SOF mission can benefit from holistic analysis of their incidents for the improvement of SOF-specific materiel, vehicles, PPE, and DOTMLPF-P considerations. JTAPIC retains SOF-experienced personnel to help this Functional Command prevent injury in this uniquely capable enterprise. JTAPIC products related to SOF can be viewed on JINCS and at SOCSocial #JTAPIC.

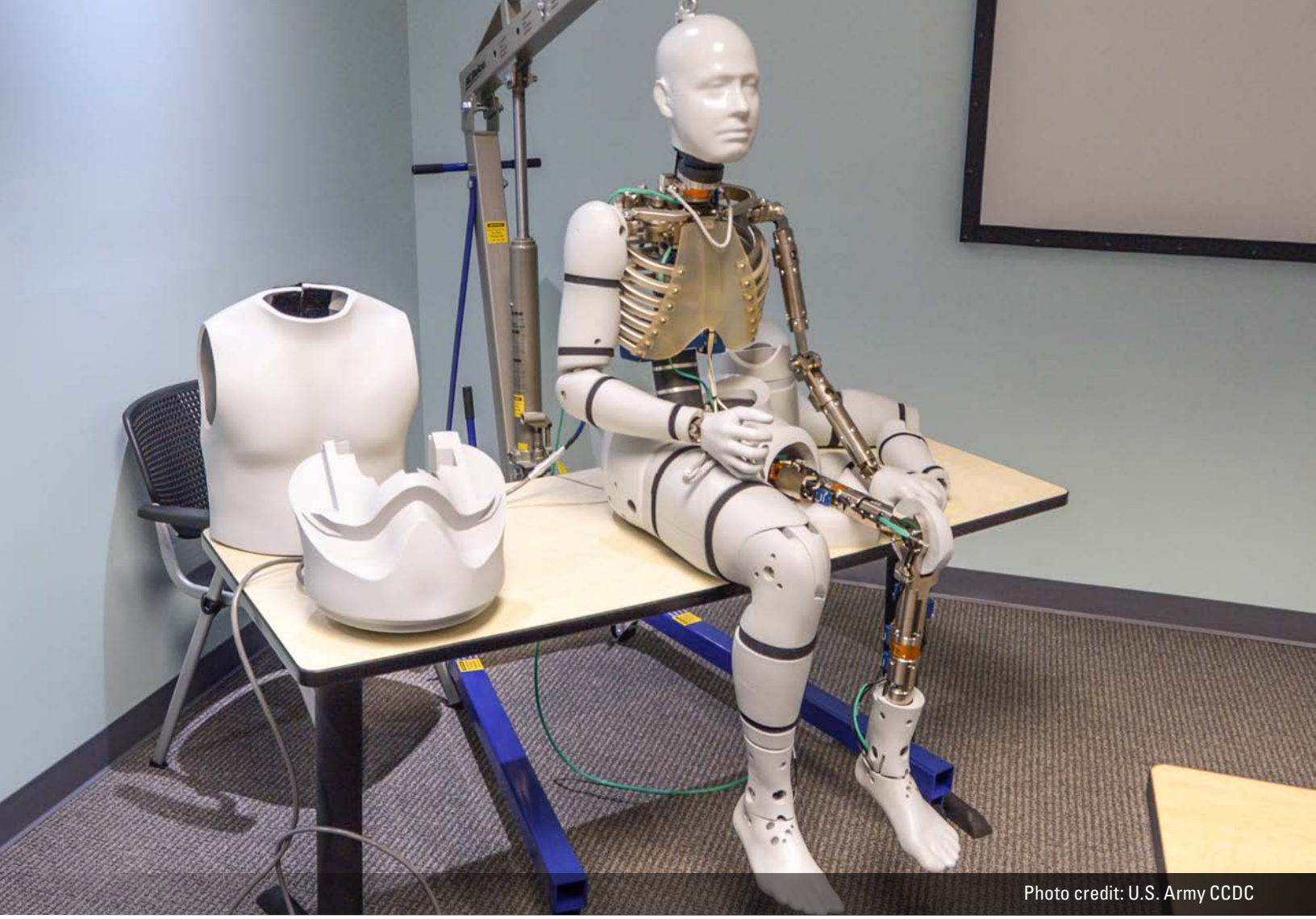


Photo credit: U.S. Army CCDC

The JTAPIC PMO continues to support the WIAMan Program and DEVCOM in its effort to expand research in soldier survivability and quality of life when subjected to the effects of underbelly blast. WIAMan has requested radiological imaging from theater combat cases to compare injury types and fracture patterns to those observed in testing. The Defense Health Agency Integrated Clinical Systems PMO has recently validated an anonymization process for this information exchange, and JTAPIC has provided the first theater cases for retrieval. The JTS has accepted these cases, and information transfer is undergoing proof of concept. Relating actual radiological images from known combat events provides validity to testing, instrumentation, and the re-creation of scenarios for the live-fire testing and evaluation community.

The U.S. Army Vets USAVS, CCDC DAC, and the JTAPIC PMO have completed initial modification of the Human Abbreviated Injury Scale (AIS) coding schema to canines. Combat incidents that involve military working dogs (MWD) often result in injuries to both handler and canine that normally serve as a functional unit. Injuries sustained by MWD handlers are categorized utilizing the AIS and communicated via Visual Anatomical Injury Descriptor (VAID) by the JTAPIC program to stakeholders across the DOD to inform DOTMLPF-P solutions for injury prevention and mitigation. Legislative efforts are ongoing (Canine Members of the Armed Forces Act, H.R. 4103) to transition the MWD designation from military equipment to Canine Service members. There is no analogous military or civilian canine trauma scoring system, canine version of VAID, or web-based application that captures, analyzes,

integrates, and stores MWD injury data alongside handler data to potentially identify canine species-specific resilience, develop canine survivability requirements, and help track outcomes for MWD and handlers as a functional unit. This effort is currently in a non-funded status; however, the initial proof of concept was well received by the SOF community. It could be made available for use in a technology transfer or cooperative research and development agreement.

JTAPIC: Forging Its Future

JTAPIC will continue to collect operational incident and accident data to inform solutions that can prevent or mitigate traumatic injury. Expertise provided by JTAPIC's 11 partner organizations results in actionable products that customers use and value in their decision-making processes to prevent or mitigate injury across the full range of military operations. As the geopolitical climate continues to change, JTAPIC is continually seeking to gain an edge through novel collaboration efforts, restructuring for efficiency, and cross-agency cooperation.

As the DOD encourages partnerships with other civilian agencies to create efficiencies and share knowledge JTAPIC is opening its doors to cross-agency collaboration. The Volpe Center is the DOT's in-house organization and resource for multi-modal systems engineering and integration, technology, analysis, planning, research, development, deployment, and evaluation. The Volpe Center's multi-disciplinary expertise in all modes of transportation is available to support topics related to vehicles and the health and safety of their occupants.

JTAPIC's close alignment with many of the Volpe Center's capabilities have presented a unique opportunity for the organization to become the first non-DOD JTAPIC partner. JTAPIC and the Volpe Center held several meetings throughout FY21 to discuss possible collaborations, such as performing engineering and human factors test and evaluation of advanced technology transportation systems using computer simulations, simulators, controlled experiments, and field operational tests and performing studies and analyses of transportation-related systems for aviation, maritime, and surface vehicles, including problem definition, safety concepts, technology assessment, test and evaluation, and impact estimation.

Photo credit: Spc. Jovi Prevot/U.S. Army National Guard

In summer 2021, the BIRCO-JTAPIC Merger was announced. Related to JTAPIC's authorities described in the beginning of this chapter, BIRCO fulfills the responsibilities and functions of the DOD Executive Agent for Medical Research for the Prevention, Mitigation, and Treatment of Blast Injuries in accordance with National Defense Authorization Act for Fiscal Year 2006, Section 256 and DOD Directive 6025.21E.

Photo credit: Master Sgt. Scott Thompson/U.S. Air National Guard

BIRCO coordinates DOD-sponsored biomedical research programs aimed at preventing, mitigating, and treating blast-related injuries; identifies knowledge gaps and shapes research programs accordingly; promotes information sharing among the operational, intelligence, medical, and materiel development communities; and facilitates collaborative research among DOD laboratories and the laboratories of other federal agencies, academics, and industry to leverage resources and to take full advantage of the body of knowledge that resides both within and outside of the DOD to accelerate the delivery of blast injury prevention and treatment strategies to Service members.

JTAPIC became a separate Program of Record in 2013 but was previously aligned under BIRCO. Given the many interrelationships between BIRCO and JTAPIC, USAMRDC decided to re-merge the two organizations under one Directorate in order to better provide the DOD with superior strategies to mitigate the effects of blast injury through research and operational analysis. JTAPIC and BIRCO will be moving forward to this end under the energetic direction of Lieutenant Colonel Jacob Johnson.

Through collaboration with the Air Force Research Laboratory, JTAPIC has been exploring options for applying machine analytic characterization, comprehension, and projection to JTAPIC datasets as well as employing mission-responsive information exchange. JTAPIC has submitted the problem statement “Medical Codes, Assemble” to the DOD Hackers for Defense, which pairs civilian, academic, and defense organizations to solve complex problems revolving around artificial intelligence and machine learning; it has been accepted for consideration. JTAPIC hopes to develop a program to solve some of its more labor-intensive data collection procedures.

Photo credit: Sgt. Matthew Hulett /U.S. Army

Photo credit: Staff Sgt. Alan Ricker/ U.S. Air Force

CHAPTER 7:

DOD BLAST INJURY RESEARCH AND DEVELOPMENT ACCOMPLISHMENTS

The DOD Blast Injury Research Coordinating Office's (BIRCO) Executive Agent (EA) support mission is to coordinate DOD blast injury research investment and leverage expertise to develop strategies that prevent, treat, or mitigate blast injuries. To inform the EA of accomplishments throughout the blast injury research community, BIRCO requested data from DOD organizations engaged in medical and non-medical blast-related research that occurred in FY21. The 142 submissions BIRCO received are reported in the following chapter, organized by the key blast injury research program areas: Injury Prevention, Acute Treatment, and Reset. These accomplishments add to the knowledge base for blast injury research, refine the strategies that prevent and treat blast injury, and help injured Service members to return to duty and improve quality of life.

The accomplishments featured in this chapter are included as they were reported to BIRCO, with as few edits as possible. Acronyms are defined within the text of each accomplishment, with the exception of select, well known acronyms that are defined once.

Please contact BIRCO for more information on any of these efforts at usarmy.detrick.medcom-usamrdc.other.medical-blast-program@health.mil.

The following table of contents provides an orientation to the accomplishments presented in this chapter.

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ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

Prediction and Risk Monitoring

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Pharmaceutical Interventions

Surgical Interventions

Secondary Injury and Comorbidities

Prolonged Care

Consortium Studies

Injury Prevention

Research on blast injury prevention considers the entire spectrum of potential injuries, from primary to quinary. There were three overarching themes to injury prevention accomplishments this year: mechanisms of injury; personal protective equipment (PPE); and prediction and risk monitoring. The design of prevention systems and strategies requires an understanding of the mechanisms of injury; thus, significant research efforts focused on determining blast injury mechanisms using animal and computational models. Studies are underway to evaluate the performance of PPE, including helmets and body armor, against blast injury and to investigate novel materials that improve injury prevention capabilities. Researchers are also implementing strategies to longitudinally monitor Service members' exposure to blast overpressure. The acquired data will help further refine 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 of injury and potential treatment targets.

Mechanisms of Injury

Pseudomonas Aeruginosa-Mediated Sepsis Following a Non-Lethal Full-Thickness Burn

According to the World Health Organization, burn-related injuries are responsible for approximately 180,000 deaths every year. Survivors of the initial burn trauma often succumb to sepsis caused by bacterial infections that arise during treatment. These secondary infections continue to result in high frequencies of burn-related deaths in low- and middle-income countries, even though advancements in burn care continue to improve in high-income countries, largely due to advanced research and burn centers that offer specialized care. The greatest danger experienced by burn injury survivors is bacterial-derived sepsis. Researchers at the University of Maryland School of Medicine and the U.S. Air Force School of Aerospace Medicine provided mouse-model evidence, for the first time, that even in the absence of infection, a subeschar seroma forms post-burn.

The seroma fills with an estimated 500 µL of fluid, 25 percent of the blood supply, devoid of red blood cells. Research has shown that seroma fluid supports vigorous Pseudomonas aeruginosa (PA) growth. In the absence of endothelial breakdown, the inflammatory cytokines and chemokines within the seroma fluid recruit immature neutrophils and monocytes to the seroma, but these immune cells fail to contain the expansion and dissemination of PA. During a crucial time in the dissemination of bacteria, this recruitment may result in promoting PA-mediated sepsis by appropriating these critical immune cells away from other tissues. This work was published in the Journal of Burn Care and Research (Brammer, et al., 2021a).

This research was supported by the Defense Health Agency, J-9.

Using a Non-Lethal Murine Flame Burn Model to Assess Host Defenses and Susceptibility to Lethal Pseudomonas Aeruginosa Infection

In 2016, 486,000 burn injuries required medical treatment in the United States. Of those, 40,000 people were hospitalized with more than 3,000 subsequent fatalities. Patients are at increased risk of sepsis and mortality from infections caused by Pseudomonas aeruginosa (PA), an opportunistic pathogen, after burn injury. Researchers at the University of Maryland School of Medicine, U.S. Air Force School of Aerospace Medicine, and The Feinstein Institute for Medical Research hypothesized that the burn initiated systemic events, which increased the host's susceptibility to PA.

Researchers performed a non-lethal 10 percent total body surface area (TBSA), full-thickness flame burn in mice, without and with subsequent PA infection. Compared with PA-infected mice

without burn injury, the 50 percent lethal dose for subcutaneous PA infection at the burn site decreased by 6-log immediately after the burn, with mortality occurring between 18 and 26 hours. By 18 hours, bacteria in distal organs were detected, concurrent with the onset of clinical symptoms. At 12 hours post-burn with infection, serum pro-inflammatory cytokines (IL-6, IL-1beta, IFN-gamma, and TNF-alpha) and the anti-inflammatory cytokine, IL-10, were first detected and continued to increase until death. Directly after burn alone, serum levels of HMGB1, a danger-associated molecular pattern and TLR4 agonist, transiently increased. However, burn injury with PA infection increased serum HMGB1 concentrations greater than 10-fold at the time of death. Infected/burned mice treated with a peptide inhibitor of HMGB1, P5779, showed increased mean survival from 23 to 42 hours. Researchers concluded that the high level of serum HMGB1, which preceded the increase in pro-inflammatory cytokines, is associated with post-burn mortality. This work was published in Infection and Immunity (Brammer, et al., 2021b).

This research was supported by the Defense Health Agency, J-9.

Time Since Injury: Post-Concussion Symptom Reporting among Military Service Members with Blast-Related Concussion

The DOD reports that approximately 400,000 Service members have sustained concussions, but little research exists that examines the role of time-since-injury on symptom presentation following blast-related concussion. Through a retrospective review of existing records in the Expeditionary Medical Encounter Database (EMED) and those who completed the Post Deployment Health Assessment (PDHA), researchers from the Naval Health Research Center, Axiom Resource Management, and Leidos examined 3,690 personnel who were injured by a blast during combat operations and their reported symptoms using a post-deployment health assessment at varying times post-injury (i.e., 1–90 days, 91–180 days, or 181–365 days). The purpose of this study was to review reported symptoms from blast-related concussions within three time points, while accounting for the loss of consciousness and mental health comorbidities. Most post-concussion symptoms were significantly elevated at 91–180 and 181–365 days compared with 1–90 days. These findings indicate a continued need to refine in-theater concussion rehabilitation and a need for further research using longitudinal data as Service members transition from combat zone to home. This work was published in the Journal of Neurotrauma (MacGregor, Shannon, & Dougherty, 2021).

This work was funded by the U.S. Navy Bureau of Medicine and Surgery under work unit no. 60808.

Contusive Injuries Alter Neuroinflammatory Changes Behavioral Responses and Motor Functions

The majority of open cranial contusion models result in considerable bleeding and eventual cavitation. While useful for the study of biological mechanisms, milder forms of injury lend themselves to greater similarity to human mild TBI conditions. A recent study developed a mild cortical impact method that resulted in local gliosis in the impact region, but no loss of neuronal tissue (Nieves et al., 2020a). With even this milder injury level mice exhibited sensorimotor impairments that were lasting in male mice but not so evident in female mice. Significantly, multiplex immunoassays were used to evaluate 18 analytes for alterations in innate immune cytokines and monocytes attractant chemokines in cortical homogenates from injured mice. As has been previously reported in clinical and preclinical TBI studies, there were robust acute elevations in analyte levels for nine of the cytokines and chemokines (CCL2, CCL3, CXCL1, CXCL2, CXCL10, interleukin [IL]-1β, IL-5, IL-6, and tumor necrosis factor alpha [TNFα]), but two chemokines did not fully resolve until two weeks after injury (CXCL2 and CCL2 [MCP-1]). Long lasting elevation was observed for inflammatory molecules: the chemokines, CCL3 and CCL10, and the cytokines IL- 1β and TNFα, that resolved

by eight weeks post-injury. Surprisingly, in this milder model there were no alterations for adaptive immune system signals (interferon [IFN]- γ, IL-10) reported in more severe TBI cases. These responses appear to not be activated when the injury severity results in intact neuronal parenchyma.

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine (grant no. G170244014).

Frontal Lobe Contusions Reduce Fear Responses and Elicit Hyperactivity in Mice

The frontal lobe is one of the most vulnerable brain regions following contusions and acceleration injuries. Researchers assessed the impact of bilateral repetitive impacts in a closed head model in male and female mice (Vu et al., 2021). Mice experienced foot shocks before testing. While injured mice exhibited continued fear on the open field, they exhibited reduced activity in the open field test and elevated zero maze compared to animals that sustained no TBI. Moreover, mice that sustained repetitive frontal cortical impacts exhibited a reduction in freezing behavior in the fear conditioning test to both cues and context and were more active in the open field test and the elevated zero maze. Overall, injury to the frontal cortical region resulted in an increase in overall activity, and female mice showed more freezing behavior than males.

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine (grant no. 310185–6.01–65310) and from the DOD and Uniformed Services University through the UCSF–USUHS Partnership: Brain Injury and Disease Prevention, Treatment, and Research; 64682-307877-2.00).

Personal Protective Equipment

Wearable TBI Prevention Device Program

The Warfighter Brain Health (WBH) Project Management Office (PMO) awarded $2.8 million for the evaluation, research, and development of a wearable TBI prevention device. The full and open contract will be awarded to Q30 Sports Science, LLC in June 2022 for the development and evaluation of the FDA-approved Q-Collar for U.S. Military operational use. This Congressionally appropriated-funded program resulted in an initial 36-month FAR-based contract that will assess Q-Collar safety and efficacy in the reduction of risk or severity of TBI when exposed to blast pressure wave events through a large animal study. Additionally, the Q-Collar performance will be assessed during extreme temperatures (operational standby and long-term storage). Tolerability will be evaluated to ensure Service member acceptance and confirm whether there is any interference with the current uniform or equipment.

This program is funded by the Defense Health Agency.

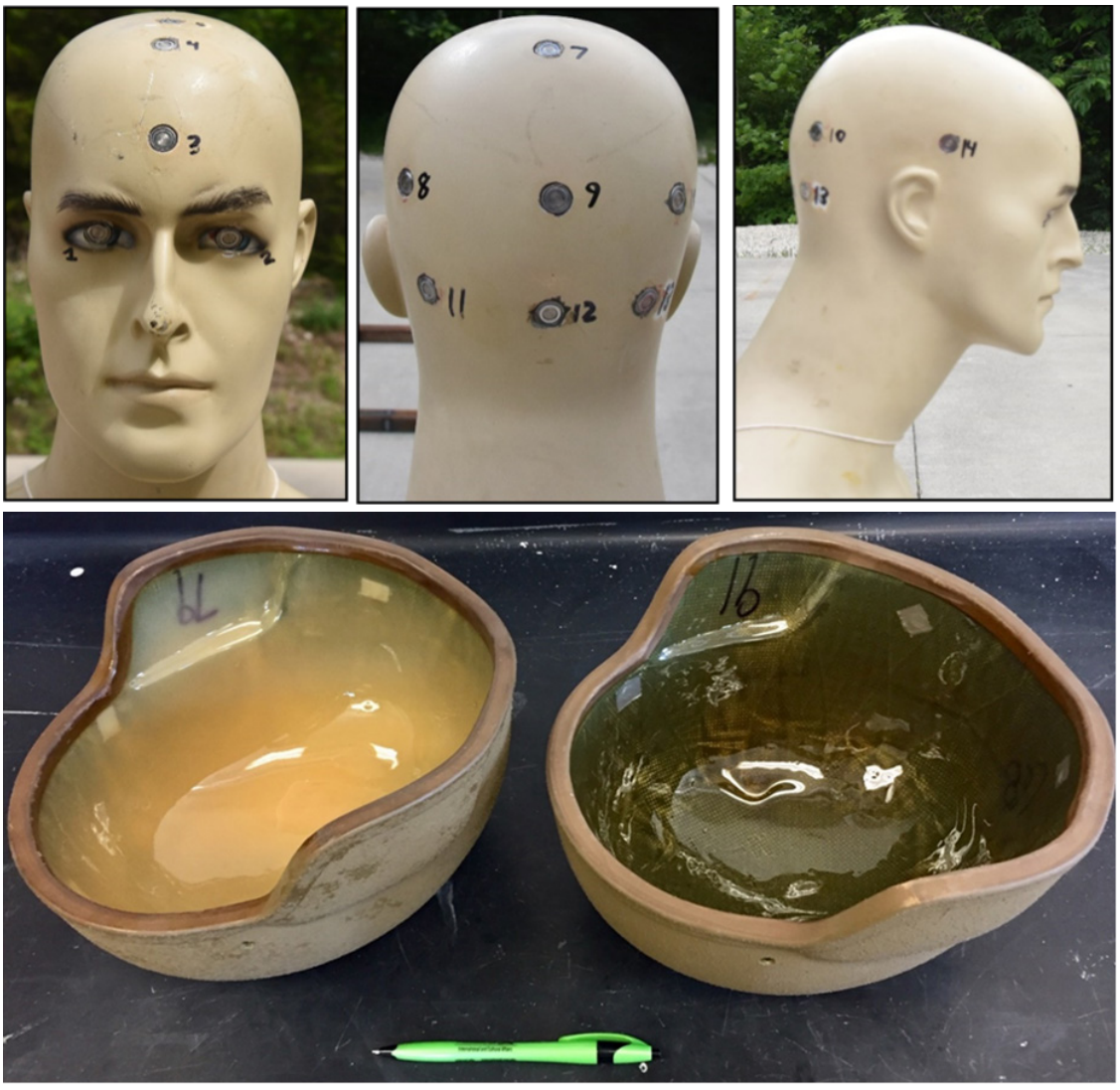
Nanostructured Composite Fluids in Liquid Body Armor

The objective of this research project was the development and fundamental understanding of impact attenuation and blast wave mitigation in the use of novel viscoelastic materials (composites of polyurethane and silicon rubber) as a helmet liner that would enable ballistic and blast protection from TBI and Behind-Armor Blunt Trauma (BABT). A systematic study on various viscoelastic materials was conducted by measuring energy dissipation factor, impact, and blast wave mitigation properties. Several Kevlar-based combat helmets were coated with a thin layer of selected viscoelastic materials. For a realistic human model, the helmets were attached to a mannequin head instrumented with 15 piezoelectric pressure sensors on various

locations (Figure 7-1). The mannequin was filled with ballistics gel to resemble a soft tissue more closely and attached to a concrete pad. Six charge sizes were used that were designed to have a static pressure between 4- and 24-pound-force per square inch (psi) in 4psi increments. Charges were constructed from Composition C-4 and hung in free air from a stand. The research team used a high-speed camera to see the interaction between the shockwave and the mannequin head and torso. Previous studies have shown that the shock passing between the head and helmet increases the pressure experienced on the back of the head more than not wearing a helmet at all. Tests revealed that the modified helmet significantly reduces pressure experienced on the head in all sensor locations compared to a standard helmet with no liner. Through full-scale experimental testing, these studies demonstrated the intended effects of the liner materials designed in the project effort. The materials effectively reduced pressure by absorbing shock rather than reflecting it from the Kevlar surface.

It is well known that wearing a helmet is not protective and can even be detrimental when a

FIGURE 7-1: Mannequin head instrumented with piezoelectric pressure sensors and Kevlar based helmet shells coated with viscoelastic materials highly effective at mitigating shock waves.



soldier is exposed to high-pressure blast waves. Such waves penetrating between the skull and the helmet are amplified through reflection (like a parabolic mirror focusing the light) and can result in an enhanced TBI. The challenge was whether lightweight viscoelastic materials would effectively absorb blast waves without a significant weight increase of the helmet itself. The research team demonstrated that the formulated viscoelastic materials as helmet liners reduced the shock wave pressure up to approximately 37 percent, while the weight increase of the helmet (just the Kevlar based helmet shell itself) was at approximately 12 percent. Such initial performance of the developed materials is quite encouraging towards mitigation of TBI caused by shock waves generated by explosives or by other means.

This research was sponsored by the Leonard Wood Institute in cooperation with the U.S. Army Research Laboratory and was accomplished under Cooperative Agreement Number W911NF-142-0034.

Development of a Photonics Smart Helmet System for Early Detection of TBI Caused by Blunt Force Impacts and Blast Overpressure Effects

TBI and mild TBI (mTBI) are an insidious problem for Service members in training and live operations. It is well established that mTBIs are among the most difficult injuries to diagnose at the time of trauma. Mild TBIs are among the least understood injuries in the military because Service members often retain "active-duty" status by avoiding self-reporting impact events that they perceive as mild and innocuous. A shortage of early detection methods imposes severe limitations on clinicians' abilities to administer the most effective therapies within the first 60 minutes following traumatic injury (i.e., the "golden hour").

Researchers at the Lightwave Technology Lab at the Missouri University of Science & Technology are developing a Photonics Smart Helmet system for early detection and preclinical diagnosis of TBI and mTBI. A Photonics Smart Helmet combines a hair-like optical fiber with the shell of a football-style or military-issue combat helmet to create a composite sensor structure. While optical fibers using Fiber-Bragg Gratings (FBGs) conventionally measure strain, bonding the fiber to the surface of a helmet enables accurate measurements of the initial shockwaves and the residual echoes of the impacts as they propagate and reverberate throughout the helmet structures and the Service member's head and neck (Figure 7-2).

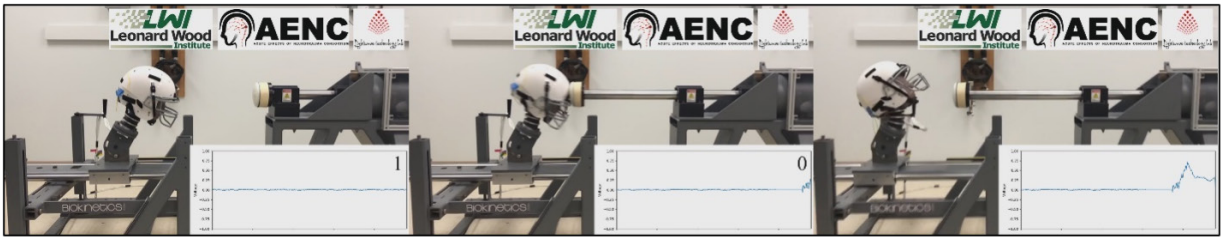
The transient oscillatory signals from an optical fiber containing only a single sensor element were found to be so data-rich that machine learning algorithms demonstrated good predictive accuracies for impact magnitude (up to $R^2 = 0.95$), impact direction (up to $R^2 = 0.95$), impact latitude/height (up to $R^2 = 0.89$), and striking implement used (frontal Regional Accuracy of at least 64.7 percent).

An improved configuration of the Photonics Smart Helmet that incorporates a second FBG sensing element placed orthogonally to the first (within the same optical fiber and using the same FBG interrogation methodology) was tested toward the end of the program and will be implemented in Phase II. The two-FBG Photonics Smart Helmet configurations exhibited improved performance of the predictive algorithms' accuracy for impact magnitude ($R^2 = 0.96$) and impact direction ($R^2 = 0.99$) without significant changes to the interrogation system (Figure 7-3).

The Photonics Smart Helmets also responds to blast overpressure events (a major cause of mTBI in the military). Explosion tests using a propane and oxygen-based improvised explosive device (IED) simulator, Composition B explosives, and TEXPAK binary explosives were

FIGURE 7-2: Left: A wireless, FBG fiber-equipped football helmet worn by a Humanetics Hybrid III 50th Percentile Male anthropomorphic test device. Middle: Several pouch variants for mounting the transceiver on the helmet. Right: Ops-Core helmet equipped with optical fiber and wireless module.

FIGURE 7-3: Frames extracted from a video of the Biokinetics Linear Impactor apparatus striking a wireless, optical fiber-equipped football helmet and the real-time transient oscillatory signal generated by the impact.



conducted at the Missouri University of Science & Technology Rock Mechanics & Explosives Research Center. In Phase II of the project, the Photonics Smart Helmet will incorporate additional fiber optic sensors based on micro Fabry-Pérot interferometers (μFPIs) to provide additional kinematic data, such as head acceleration and rotation, and direct measurement of blast overpressure events. The tailored machine learning algorithms will employ existing clinical data to generate preclinical mTBI treatment recommendations in real-time for Service members in the field.

This research was sponsored by the Leonard Wood Institute in cooperation with the U.S. Army Research Laboratory.

Improvement and Validation of 3D Printed Human Temporal Bone or Human Ear for Standardized Testing of Hearing Protection Devices in Blast Exposure

Two hearing protection devices (HPDs), a standard foam earplug and Lyric hearing aid, were used for testing the protective function of the 3D printed temporal bone (TB) during blast. Results from this study at the University of Oklahoma show that the pressure measurements in the 3D printed TB were well within the mean and standard deviation of the published data from tests performed in human cadaveric TBs, demonstrating that the 3D printed TB is a valid model for testing HPD designs. The 3D printed TB developed in this study provides an accurate and cost-effective evaluation of HPDs' protective function against blast overpressure exposure, with the potential to perform as a TB model for research in ear biomechanics for acoustic transmission. A major outcome from

this research project is the characterization of HPDs' protective function in blast exposure through experiments with human cadaver ears, animal ears, and the 3D printed human ear or TB; and the simulation in a finite element (FE) model. The standard criteria for HPD design and evaluation, based on a nonlinear FE model of the human ear and biomechanics of tissue injury after blast exposure, can be delivered. Several notable publications have resulted from this work, including Journal of Biomechanical Engineering (Brown, Bradshaw, & Gan, 2022) and Annals of Biomedical Engineering (Brown, Ji, & Gan, 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Military Operational Medicine Research Program/ Joint Program Committee-5.

Effects of Personal Protective Equipment on the Spinal Column Loads from Underbody Blast Loading

Underbody blast loading happens to mounted Service members in combat-related events. These events are associated with injuries to the musculoskeletal system that result in fractures to the spinal column. Biomedically, injuries are quantified using the transmitted forces and bending moments that occur during an event. The use of personal protective equipment, i.e., head supported mass, in the form of a helmet and body armor vest, imparts additional loads to the mounted Service member and alters the internal spinal forces and moments. The change in load paths depends on the spinal region impacted and equipment used: thoracic and lumbar spines closer to the body armor and cervical spine closer to the head supported mass. The purpose of this study, conducted by researchers at the Medical College of Wisconsin, was to determine the force and moment distributions for the three spinal regions (cervical, thoracic, and lumbar), while accounting for the effect of the personal protective equipment. The methods used in the study included a human body finite element model; the seated model-occupant was restrained with a military harness. The model-occupant was subjected to underbody blast loading, and forces and moments were determined for all spinal regions. A military helmet and a military body armor vest were simulated. After stabilizing the model, the same acceleration pulse profiles were applied to the mounted Service member model-occupant, and forces and moments were determined for the 3 spinal regions. Results showed that personal protective equipment accentuated forces and moments in the cervical and thoracic spines and reduced forces and moments in the lumbar spine, while acceleration morphologies remained similar in all regions. In addition, the cervical spine responded with compression-extension, while thoracic and lumbar spines responded with the compression-flexion mode of kinematics. Force and moment variations in the spinal regions and their respective modal changes delineate the role of personal protective equipment on load transfer within the human vertebral column. As the study simulated underbody blast scenarios, results are applicable to military events and can be used to assess the safety of Service members. In addition, recognizing the role of personal protective equipment on alterations in load transfer within the spinal column, studies applicable to Service members who have surgeries, such as artificial discs, can be advanced. Artificial discs are known to alter load paths in the anterior and posterior cervical columns and affect the response of the cervical spine. Because the discs approved by the U.S. Food and Drug Administration have differing designs, such as metal on metal and metal on polymer implants, it is important to analyze loads and motions under physiologic scenarios, which include the effects of differing sizes of head supported mass on male and female Service members. This research was published in the Proceedings of the International Mechanical Engineering Congress & Exposition 2021, Umale, S., Humm, J., & Yoganandan, N. (Eds.). (2021),

IMECE2021. The American Society of Mechanical Engineers.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Military Operational Medicine Research Program/Joint Program Committee-5.

Validation of Electromechanical Hearing Protection Methods and Development of a Hearing Protection Selection Tool

Researchers at Applied Research Associates (ARA) are developing methods to evaluate and quantify specific characteristics of hearing protection devices (HPDs) for specific operational use cases. Additionally, the ARA team seeks to move away from time-consuming and expensive human-based HPD evaluation to methods that automate HPD evaluation based on electromechanical test methods and standardized performance characteristics. The research outcome would be a software decision aid tool that would enable military leaders to tailor appropriate HPDs for mission requirements at lower costs for HPD vendors and end-user communities. The ARA team actively engaged with various DOD stakeholder communities, such as the Hearing Center of Excellence and the Defense Logistics Agency, for input on developing the hearing protection selection tool. Ongoing work includes a number of activities including validation of HPD electromechanical test performance with human subject perception.

This effort was supported by the Joint Warfighter Medical Research Program with program input by the Military Operational Medicine Research Program/Joint Program Committee-5.

Phase I STTR for the Development of an In-Ear Exposure Sensor with Integrated Noise Attenuation and Communications Capabilities

There have been multiple attempts to record exposure conditions related to mTBI in the military. Existing technologies usable in a military environment primarily measure blast exposure or suffer from poor coupling to the head and require substantial post-processing of the data to correlate the sensor motion to head motion. In-ear based systems may provide a reliable solution for measuring both head acceleration and blast exposures. However, current in-ear sensor systems do not combine head kinematic sensing technology with other essential functions that an earpiece must provide to the Service member: communications and continuous steady-state and impulse noise attenuation. As a part of a Phase I Small Business Technology Transfer Program (STTR) from the U.S. Army Aeromedical Research Laboratory (USAARL), two companies were selected to develop, demonstrate, and deliver an in-ear device that integrates three functions: 1) sensing and recording head response to both blast and blunt impact events, 2) communications, and 3) continuous and impulse noise attenuation. These two companies were Diversified Technical Systems (DTS) and Paxarius.

Through this Phase I STTR, researchers at DTS collaborated with the University of Virginia to develop an In-Ear Exposure Sensor (IEES). DTS was responsible for the design and specifications of the sensor, and UVA developed a test surrogate and testing fixtures. Through this effort, a functional prototype was developed and tested in operationally-relevant conditions. The developed IEES was tested using both a linear impactor to measure kinematic responsiveness to direct blunt impacts and a shock delivery system to measure the responsiveness to blast exposures. In both testing scenarios, a modified Hybrid III with an ear surrogate was used to place the IEES. After testing was completed, a transfer function was developed

relating in-ear sensor data to head center-of-gravity data. Overall, this effort produced a functional prototype capable of measuring head kinematics during both blunt impact and blast exposures.

Researchers at Paxarius collaborated with Prevent Biometrics, the Medical College of Wisconsin, and Iowa State University to develop a hearable (H3) system for impact and blast kinematic measurements. Through this effort, researchers incorporated earplug accelerometers into both foam and fluidic earplugs. Additionally, this research showed that earplug accelerometers can capture rigid-body head motion during both blunt impact and blast exposures. Testing was conducted using drop tests, blasts from a shock tube, linear impacts, exposures on a shaker table, and sound waves. Results determined that fluidic earplugs with a single accelerometer have the potential to provide sufficient accuracy for head kinematics and were associated with comfort and ease of use.

Overall, this Phase I STTR showed two proof-of-concept devices that provide the ability to monitor Service members for potential TBI during combat operations. This increased monitoring will allow Service members to receive medical attention sooner to address potential injuries prior to any additional or compounding injuries. By quickly addressing injuries, a Service member's return to duty may be accelerated, thus maintaining combat power and increasing Service member lethality. Continued development efforts are being explored.

This work was funded by the Defense Health Agency Small Business Innovation Research/ Small Business Technology Transfer (STTR) Program Office through a Phase I STTR.

Soft-Armor Vest Effectiveness and Intrathoracic Biomechanics in Rodents Exposed to Primary Blast

The biomechanics and efficacy of personal protective equipment in mitigating blast overpressure remain unclear. Researchers at Walter Reed Army Institute of Research have defined biomechanical changes of intrathoracic pressures in response to blast wave (BW) exposure and evaluated the effectiveness of a soft-armor vest (SA). Sprague Dawley rats (n = 15) were surgically instrumented with pressure sensors inside the thorax and exposed to a range of pressures (33, 46, 63, or 108 kPa) off-axis in a holder (left side of the animal toward BW) with SA and without SA (woSA) chest protection inside the Advanced Blast Simulator (ORA Inc., Marion, NC).

At least 11 data points were recorded at each pressure using a TMX-18 data acquisition system (Astronova Inc., West Warwick, Rhode Island) sampled at 800,000 Hz. Pressure traces were analyzed using MATLAB (MATLAB R2016b, Natick, Massachusetts). Researchers removed high fluctuation noise by using a moving average to filter the data for analysis of impulse and duration for positive and negative pressures of the BW. Significant increases in positive rise time, negative peak pressure, and negative impulse in the thoracic cavity were observed compared to the BW. Esophageal pressures consistently increased when compared to carotid and the BW for blast parameters (except positive impulse, which decreased). Power spectral analysis was minimally altered by the addition of SA (less than 4.5 percent energy). Overall, SA did not alter the majority of biomechanical parameters, and the superficial thorax (carotid) was relatively comparable to the BW compared to deeper thoracic structures (esophageal).

This study uniquely compares pressure parameters in a living system, establishes relationships between the external primary BW and the internal pressures in the thoracic

cavity, and evaluates the effectiveness of an SA vest at altering these pressure changes. Novel analyses evaluate pressure parameters and the frequency content of the BW to identify similarities and differences between pressure groups and between SA and woSA. Data from this study, which show few changes in blast biomechanics in the presence of an SA vest, upon validation with larger species could provide important insights shaping current guidelines for primary blast protection in addition to vest protection against ballistic and penetrating injury.

This research is funded by the Congressionally Directed Medical Research Programs–Peer Reviewed Medical Research Program under award W81XWH1920058.

Prediction and Risk Monitoring

Mechanisms of Center Auditory Pathways in Blast-Induced Hearing Loss

As a consequence of blast overpressure exposure, Service members with hearing loss may have difficulty communicating on a radio, maintaining situational awareness, localizing sounds, and maintaining lethality. Researchers at the Walter Reed Army Institute of Research (WRAIR) have gained considerable insights into the mechanisms of blast-induced hearing loss (BIHL), with the successful development of rat and mouse models of blast injury employing an advanced blast simulator. Hearing thresholds and ear pathological and molecular changes following blast exposure have been discovered as the peripheral mechanisms of BIHL.

To address the possibility that shockwaves impair sound processing centers in the brain, researchers at WRAIR and Lieber Institute for Brain Development at Johns Hopkins University evaluated the functional connectivity from medial geniculate nuclei (MGN) to the auditory cortex (AC) using optogenetics assay in combination with whole-cell patch-clamp electrophysiological recording. Data showed that input-output relationships between stimulation intensity and excitatory postsynaptic potentials (EPSPs) at the medial MGN-AC projections in the AC were significantly reduced at one, three and seven days after blast exposures. No significant change was found at 28 days post-blast exposures, indicating an apparent recovery from abnormal (compromised or dysfunctional) circuits among neurons and glia. Synapse is essential to the transmission of electrical signals between two neurons. To determine the pathological alterations in the AC region that are associated consistently with the functional changes, the researchers examined the dendritic spines which serve as the storage sites for synaptic strength. Transgenic mice (Thy1-YFP) were employed. Significant increases in the total number of dendritic spines at four hours and seven days post-blast were predominantly evident as the immature types of

Photo credit: U.S. Army

stubby and thin spines, with no significant change observed in the number of mushroom type. Consequently, the ratio of mushroom-type spines decreased. The increase in the stub type of spine persisted to seven days post-injury. Data indicated the synaptic transmissions in excitatory neurons were quite sensitive to blast insult. At one day post-injury, synaptic proteins synapsin and neurexin at the pre-synapse and neuroligin at the post-synapse were significantly reduced.

These findings revealed that blast injuries to the center auditory pathway may also contribute to BIHL and communication deficits. These findings also reveal an optimal therapeutic window for a therapeutic intervention after blast exposures.

This work was sponsored by the U.S. Army Medical Research and Development Command.

Concussion Dosimeter Program

This Defense Health Agency-funded program in the Warfighter Brain Health (WBH) Project Management Office (PMO) oversees the advanced development needed to field wearable blast overpressure dosimeters to the conventional forces. WBH is collaborating with the USSOCOM Blast Exposure Monitoring program on market research, technological maturation, and testing and evaluation. WBH is also partnering with the Walter Reed Army Institute of Research to identify Service member needs and obtain feedback on prospective candidates.

This project is supported by the Defense Health Agency and the Military Operational Medicine Research Program.

Blast Sensor Technologies Comparative Study

U.S. military personnel are exposed to blast and high-sound exposures in combat and training operations. These exposures arise from multiple sources, such as improvised explosive devices (IEDs), ordnance (breach explosives, hand grenades), and heavy weapon system (shoulder-fired weapons, high-powered rifles) operations that can have deleterious effects on military personnel. The National Defense Authorization Act FY20, Sec.716, requires the DOD to include blast exposure history in the medical records of Armed Forces members. Measuring blast overpressure in combat and training operational environments is very challenging due to Service member orientation to the exposure and protocols that are followed. Blast exposure on the individual Service member needs to be measured with adequate precision, accuracy, and sensitivity in operational environments.

The purpose of this project, conducted by researchers at Walter Reed Army Institute of Research, Combat Capabilities Development Command (DEVCOM), and Naval Submarine Medical Research Laboratory, is to compare the ability of commercially available and emerging wearable blast sensor technologies to capture blast events at various intensities (approximately 2-20 psi) and orientations to the blast wave (0˚, 45˚, and 90˚). The blast sensor technologies being compared are from Black Box Biometrics, L3 Technologies, Med-Eng (blast tracker I and II), and Advanced Materials and Devices Inc. For example, a blast sensor that is oriented toward the blast wave will produce a different reading when compared to blast waves that contact the sensor at a different angle (e.g., 45˚). Some blast overpressure sensors are very sensitive to blast orientation, while others underestimate the blast exposure. Additionally, some manufacturers require each Service member to wear multiple blast sensors that are specifically located on the chest, helmet, and both shoulders, which can be cost prohibitive. Wearing multiple sensors practically guarantees that each sensor will produce a unique overpressure reading for each blast. The differences among these readings could make the sensors confusing as a leadership tool to monitor blast. As expected, we have learned, in a field research setting, that it is common for a

Service member to be exposed to blast and to have each of the sensors being worn provide a unique overpressure reading. Thus, it is very difficult to approximate the actual operational exposure.

In this study, a state-of-the-art Advanced Blast Simulator is being used to evaluate and understand the performance of these sensor technologies. The critical ambient blast wave loading is recorded by a pitot probe (industry standard), which has two sensors to measure incident (static) and total (stagnation) pressures, to compare the recordings from these wearable blast sensors in incident (side-on) and total (face-on) pressure configurations. The deliverable will be a demonstration of the optimal technology to record blast overpressure that can potentially be used to monitor blast exposure as a wearable sensor for Service members (analogous to a radiation dosimeter). A side-by-side comparison of these five sensors, in a controlled environment, will provide the necessary information to evaluate their relative merit.

This research was supported by the U.S. Army Foreign Comparative Technology Program.

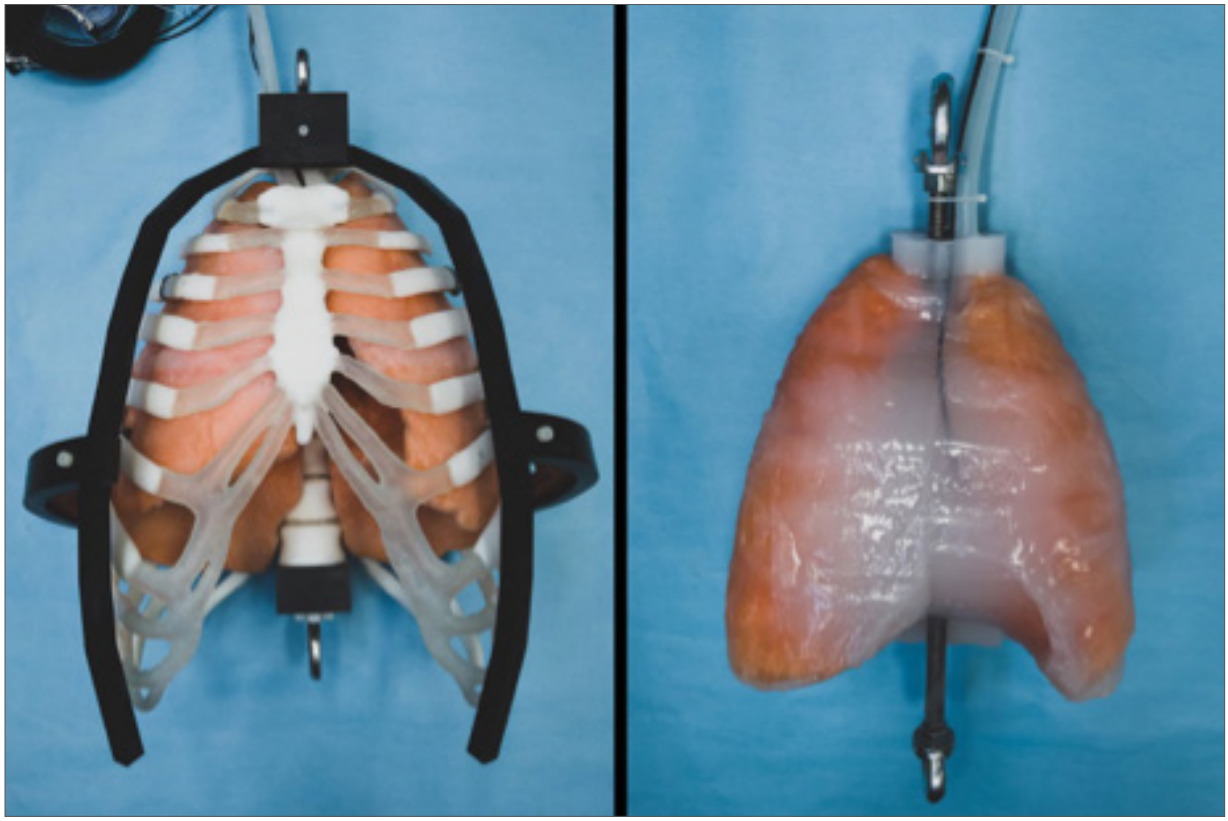
Lung Blast Simulation to Predict Injury

Scientists at the Naval Submarine Medical Research Laboratory (NSMRL) developed mechanical/physical models to illustrate the response of internal air-filled structures to underwater blasts to aid in predicting what might occur in humans (Figure 7-4). The research team plans to use the physical models to help develop and improve computational models that predict injury to humans from underwater blast exposure.

The goals of this project are to 1) characterize the internal pressure response of a solitary pair of lungs and lung/rib cage physical models to small charge blast and other sound sources, 2)

FIGURE 7-4: NSMRL's two lung simulants

On the left is the lung with a rib cage. On the right is the bare lungs. Both simulants have blast sensors integrated into each lobe of the lung to capture internal pressure measurements during exposure to underwater blast insult.



visualize the external behaviors of lung models, including the interaction of the lung with the rib cage via high-speed videography, and 3) compare the results of "standalone" models to NSMRL's QUantitative INstrumented Torso (QUINT) human torso model that has a pair of internal lung simulants.

The lung models were developed utilizing computed tomography (CT) scan data of 50th percentile male human lungs with equivalent air volumes. The models use synthetic materials with similar viscoelastic properties to human lung tissue. The lung models are outfitted with two internal pressure sensors, placed within each lung, and strain gauges on the rib cage section. The research team documented the effects of small charge explosives detonated underwater near the instrumented lung physical models.

Preliminary results suggest similar internal pressure responses in the lung models that were observed in QUINT's lungs. A more detailed analysis of the lung models' responses is forthcoming. Additional planned studies will be conducted to characterize the physical models' response to seismic air guns to evaluate the low-frequency resonance of air volume within each of the lungs. Based on previous measurements with QUINT, the research team expects the lung resonance to be around 50 Hz, which is similar to measurements of human lung resonance conducted underwater. It is likely that the presence of the "tissue layers" surrounding the thoracic cavity in QUINT will affect its lung motions which could shift the resonance frequency.

QUINT has proven valuable in previous studies for measuring the potential human response to underwater blasts. However, its opaque outer tissue layers prevent visualization of lung motion. This limitation reduces the research team's ability to predict lung response, such as injuries associated with lung overexpansion and lung interactions with the rib cage. These lung models will fill this data gap. In addition, due to the lung's size and portability relative to QUINT (which is designed to mimic a 50th percentile male), deployment and data collections may prove easier in challenging environments (e.g., open ocean). The research team's goal is to use key injury and acoustic metrics from these initial tests to inform the development of an underwater version of the blast test device.

This effort was supported by the Joint Program Committee-5.

Capturing Acoustic Propagation of Blast Waves in a Shallow Water Beach Environment

Scientists at the Naval Submarine Medical Research Laboratory (NSMRL) were invited to participate in an Airborne Mine Neutralization System (AMNS) test by N7 Naval Surface and Mine Warfighting Development Center, Mine Warfare Division, Coronado Island. NSMRL's role in this exercise was to capture the underwater blast acoustics produced by the AMNS deployed technologies. NSMRL captured acoustic propagation of the blast wave as it approached a shallow water beach environment (Figure 7-5). The effort used inert mines as a practice run for a planned 2021 live-fire exercise.

The Naval Surface Warfare Center – Indian Head Explosive Ordnance Disposal Technology Division 60-series publication A-1-1-37 provides guidance for minimum recommended safety standoff distances for divers swimming in the vicinity of underwater explosions. The objective of NSMRL's involvement in this exercise was to evaluate the applicability of the existing A-1-1-37 approach for use in beach environments. The data collected in these AMNS training events will be used to test and may lead to recommended updates to the A-1-1-37 standoff tables.

Using the data collected in this exercise, three simple models of blast wave propagation were tested: 1) spherical spreading, 2) Arons (1954), and 3) Rogers (1977). These models can predict

FIGURE 7-5: NSMRL's Aquarius sensor node was deployed in the raft and anchored at a measurement location during the Mine Neutralization Exercise 2020 trials.

blast wave metrics, such as peak pressure and A-duration impulse, that are used to provide safety guidance for human swimmers and divers. The models all overpredicted the peak pressure and A-duration impulse measured in this beach-type environment. The outcome implies that the existing models will provide conservative guidance, under the existing assumption that peak pressure and A-duration impulse are the relevant criteria for injury prediction in this type of environment. However, the failure of these models to accurately predict the observed waveform metrics provides motivation to improve the understanding of underwater blast injury mechanisms so that more robust risk estimates can be made for beach-type shallow water environments.

The 2021 exercise was postponed until 2022. NSMRL made progress by completing the report from the 2020 exercise. A test plan was developed to maximize the data that will be collected in 2022.

This effort was supported by the Joint Program Committee-5.

A Pelvis-Lumbar Spine Model to Develop Human Pelvis Injury Risk Curves from Underbody Blast Impact

Injury risk curves (IRCs) are needed to understand the mechanism of injury, develop human tolerance, and improve the safety of the Service member. It is well known in medical literature that underbody blast loading during combat events results in fractures, more often to the lower extremities, pelvis, and spine than other body regions. These injuries affect the field performance of the Service member and their quality of life, in addition to financial implications. As the underbody blast loading imparts loads to the pelvis and spine via the seat to the seated Service member, it is necessary to use both the pelvis and lumbar spine components to determine the tolerance to injury under this loading vector, i.e., the impact of axial loading to the spine via the pelvis. Furthermore, because the human pelvis is the first component to absorb the energy, load transmission and fracture to this body region should be delineated to develop IRCs, which is the purpose of the present study, conducted by researchers at the Medical College of Wisconsin. The methods used to develop the curves included an analysis of experimental data

Photo credit: Spc. John Lytle/U.S. Army

from 26 post-mortem human surrogate lumbo-pelvis complexes. IRCs in the form of mean and 95 percent confidence intervals were based on parametric survival analysis, and the optimum risk function was based on the Akaike information criterion. Results showed that at mid-risk level, the resultant and axial forces were 6.6 kN and 5.9 kN for the lower severity fracture, and 8.4 kN and 7.5 kN, respectively, for the higher severity fracture. Based on the confidence interval sizes, the qualities of the IRCs were found to be in the good to fair range for both fracture severities. Increased injury severity also resulted in increases of biomechanical force metrics for both fracture severities. This is the first analytical study to develop axial and resultant force-based IRCs, which define human tolerance to pelvic injuries from vertical impacts, simulating underbody blast loading using parametric survival analysis. These data are useful to advance the safety of Service members when they experience vertical loading to the seated pelvis. This research was published in the British Medical Journal (Yoganandan, et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Military Operational Medicine Research Program/Joint Program Committee-5.

Male and Female Spinal Injury Risk under Vertical Loading

In FY20, the U.S. Army Aeromedical Research Laboratory (USAARL) delivered recommendations for seat performance acceptance thresholds to control occupant risk of spinal injury from vertical accelerations seen during survivable crash events for the mid-size male. These recommendations were developed from injuries in male whole-body post mortem human subjects (PMHS) and compared to responses of 50th percentile male anthropomorphic test devices (ATDs). Vertical impact exposures approached but did not exceed the seat pan response requirements outlined in Military Specification-58095A. The number of female Service members occupying aviation and combat positions has increased, but sex-related occupant protection standards have not followed suit. Sex-dependent anatomical differences in

the pelvis and lumbar spine could affect the thoracolumbar tolerance to vertical compressive loads. To address this knowledge gap, interim injury assessment reference values (IARV) were developed for the Hybrid III 5th percentile female ATD lumbar load cell. An experimental approach was conducted that consisted of performing matched tests with the Hybrid III 5th percentile female ATD against the prior male PMHS tests. The resulting IARVs were scaled by 85 percent to adjust for known vertebral body strength differences between males and females. Use of this interim IARV will reduce the risk of female occupants sustaining thoracolumbar injuries that would be detrimental to their mission and livelihood. Additional testing is planned in FY22 with female PMHS, which will be used to validate the interim recommendation or provide critical data to support revising the interim recommendation. The generation of sex-specific IARVs and injury risk tolerances, as well as increased understanding of the differences in injury tolerance due to sex, will inform the crashworthiness components of Future Vertical Lift (FVL) platforms. The knowledge gained can also be extended to inform ongoing research for Under Body Blast related pelvis and spinal injury.

This work is supported by the Military Operational Medicine Research Program with strategic alignment to Future Vertical Lift Research Program.

Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study (TIDOS–IDCRP)

In response to a need for prospective, standardized collection of infection-related data from combat casualties, TIDOS was initiated on 1 June 2009 to further the understanding of the infection burden in combat casualties. The primary objective of TIDOS was to describe the infectious disease epidemiology of deployment trauma-related injuries or other nosocomial infections among wounded military personnel. The specific aims of the study were to 1) describe epidemiology (burden), clinical characteristics, and outcomes of wound infections among military personnel; 2) evaluate microbiologic factors associated with colonization or infection and their impact on clinical course, response to antimicrobial exposure, and role in transmission; 3) evaluate optimal treatment duration and effectiveness of novel strategies and therapies for treatment and prevention of wound infections (with emphasis on multidrug-resistant [MDR] infections) in high-risk trauma; and 4) assess Military Health System antibiotic stewardship, to include adherence and outcomes of Joint Trauma System Clinical Practice Guidelines, in support of the Combating Antibiotic-Resistant Bacteria U.S. Initiative.

The TIDOS is a multi-center observational study of short- and long-term infectious complications following deployment-related trauma. Trauma-related data were collected from the DOD Trauma Registry, while infection-related data were prospectively and systematically collected through the supplemental Infectious Disease module. Prior to discharge from a participating military hospital in the continental United States, patients were given the opportunity to enroll in the follow-up cohort of TIDOS. In addition, patients enrolled in the TIDOS follow-up cohort who entered the U.S. Department of Veterans Affairs (VA) health care were given the opportunity to consent to additional follow-up through data abstraction of VA health care records. The participation population included military personnel or DOD beneficiaries (≥ 18 years of age) wounded during deployment (1 June 2009 – 31 December 2014) who received care at Landstuhl Regional Medical Center before being transitioned to a participating military hospital in the continental United States (Walter Reed National Military Medical Center and Brooke Army Medical Center).

There were several reportable outcomes for the TIDOS study, such as examining 51 patients with *Klebsiella* spp. infections (82 percent with blast-related trauma) found that 45 percent had initial infecting *Klebsiella* isolates classified as MDR, with no significant difference in the timing of isolate

recovery and injury severity between the patients with and without MDR *Klebsiella*. Approximately 31 percent of patients had serial isolation of *Klebsiella* spp. with no significant difference in injury severity between those with serial isolation of *Klebsiella* spp. and those without. While not statistically significant, there was a trend towards higher mortality (19 percent) among those with serial isolation compared with patients who only had initial isolation (3 percent, $p = 0.07$). A comprehensive evaluation of 146 patients with infections attributed to *Pseudomonas (P.) aeruginosa* was also completed. Approximately 90 percent of the patients with *P. aeruginosa* infections sustained blast trauma, which was significantly higher compared to patients with infections attributed to a pathogen other than *Pseudomonas* spp. (73 percent; $p < 0.001$). Approximately 10 percent of patients had MDR *P. aeruginosa* with significantly higher injury severity compared to patients with non-MDR *P. aeruginosa* (median injury severity score of 50 versus 33; $p = 0.001$). Among patients with serial isolation of *P. aeruginosa*, there was a high level of emergent antimicrobial resistance.

Outcomes were examined among 341 patients (72 percent with blast trauma) who received at least one combat-related exploratory laparotomy. Forty-nine (14 percent) patients developed at least one abdominal surgical site infection following laparotomy. Risk factors included having a non-abdominal infection prior to the development of the abdominal surgical site infection and sustaining either colorectal or duodenum injuries. When deep incisional or organ space infections were considered (superficial surgical site infections [SSIs] excluded), sustaining improvised explosive device (IED) blast-related trauma compared to other penetrating injury mechanisms (i.e., gunshot wound) was associated with a lower likelihood of infection risk. A likely explanation is that the penetrating injury mechanisms, such as gunshot wounds, may have resulted in greater intra-abdominal contamination and predisposed the combat casualties to a higher risk of organ space and/or deep incisional SSIs.

Outcomes were also assessed among 87 combat casualties who received at least one anastomoses, of whom 53 percent sustained blast trauma, primarily via an IED. Thirteen (15 percent) patients had anastomotic failure, with 21 percent sustaining blast trauma compared to 57 percent with blast trauma among the patients who did not have anastomotic failure ($p = 0.081$). There was no significant difference in anastomotic type between those with and without failure. Patients who did have anastomotic failure had a greater number of anastomoses ($p = 0.030$) and required more laparotomies ($p = 0.013$) compared to patients who did not have anastomotic failure. Twenty-five percent of patients developed an abdominal surgical site infection, with 38.5 percent and 23 percent among those with and without anastomotic failure ($p = 0.236$). While the overall proportion of abdominal surgical site infections was not significantly different between the groups, after restricting to deep incisional and organ space infections (excluding SSIs), there was a trend to more SSIs in the group with anastomotic failure (38.5 percent versus 16 percent; $p = 0.062$). Whether the use of vancomycin and piperacillin-tazobactam combination therapy (VPT) was associated with the occurrence of acute kidney injury was also examined among 268 combat casualties (81 percent with blast trauma): 61 who received VPT (66 percent with blast trauma) and 207 who received vancomycin plus other broad-spectrum beta-lactam (VBL) antibiotics (85 percent with blast trauma; $p = 0.001$). Twenty-eight (10.4 percent) patients developed any stage of acute kidney injury, with 13 percent occurring in the VPT group and 9.7 percent in the VBL group. Utilization of VPT, loss of more than one limb, and exposure to aminoglycosides were independently associated with a higher risk of developing acute kidney injury in the multivariate model, while the

use of mechanical ventilation and administration of non-steroidal anti-inflammatory drugs were associated with a lower likelihood. Sustaining blast trauma caused by an IED was associated with an increased risk of acute kidney injury in the univariate model; however, the variable was not retained in the multivariable model. It is important to note that while the incidence of acute kidney injury in the VPT group was 13 percent, the severity was low and had a short duration, with nearly all patients returning to their baseline renal function.

Nearly 50 percent of wounded military personnel who were medically evacuated to Landstuhl Regional Medical Center during the TIDOS study period sustained blast-related trauma, with 65 percent of those transitioned to participating hospitals in the continental United States being blast-injured. This high proportion of patients with blast-related polytrauma (frequently severely or critically injured) allows for the comprehensive examination of epidemiology (including risk factors), infection syndromes, microbiology, and outcomes among patients with differing injury patterns and injury severity. During the past year, analyses have focused on infectious complications following exploratory laparotomies, penetrating central nervous system injuries, and burns. A comprehensive evaluation of combat casualties, largely blast injured, with infections attributed to *Enterobacter* spp. are being examined. In addition, the healthcare utilization and cost of combat casualties are also being assessed. These findings may provide support for the development of clinical practice guidelines and process improvements.

This study was funded by the National Institute of Allergy and Infectious Diseases; Uniformed Services University of the Health Sciences, Health Services Research Program; and Military Infectious Diseases Research Program.

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 academia and the private sector are improving preclinical models, developing new diagnostic tools, and testing new pharmaceutical and surgical interventions to treat blast injury. The combined research efforts will improve our understanding of the capabilities and limitations of current technologies; design of new tools; methods to validate injury mitigation in the pre-hospital setting; and diagnostics and clinical guidelines for the acute treatment of blast injuries. Acute treatment accomplishments from FY21 are organized into four categories: assessment; anatomical and injury models; pharmaceutical interventions; and surgical interventions.

Assessment

MicroRNA Biomarkers to Detect Chronic Blast-Related TBI in Service Members and Association with Long-Term Outcomes

The incidence of TBI in Service members has seen a significant increase in the past decade with the operations in Iraq and Afghanistan. Injuries from single or repetitive blast explosion are among the most common type of brain trauma in the U.S. military. Multiple studies have indicated that TBI induced by exposure to repetitive blasts is frequently associated with an increased risk of mental health disorders. Lack of a biomarker for chronic TBI that can track the effectiveness of treatment further impedes the translation of potential treatments to the clinical setting to improve long-term TBI outcomes. A noninvasive, sensitive, and specific diagnostic assay is desirable, which can be used assess the therapeutic efficacy of the treatment for TBI. Researchers at the Uniformed Services University of the Health Sciences conducted research to identify microRNA (miRNA) biomarkers for chronic

TBI in Service members exposed to blast and impact TBI and to evaluate whether the blood-based biomarkers correlate with the clinical outcomes observed in the patient cohorts.

The observational study recruited Service members with a prior history of single or multiple mild TBI(s). The participants in the TBI groups sustained these multiple injuries in incidents that include motor vehicle accidents, falls, fights, and blast explosions. Four different patient cohorts were studied for miRNA expression: 1) Service members with no history of TBI or Posttraumatic Stress Disorder (PTSD) (Control), 2) Service members with one or two incidences of TBI, 3) Service members with three or more incidences of TBI, and 4) Service members with TBI and PTSD. MiRNA profiling was performed using a multiplex platform, and validation of the data was performed using droplet digital polymerase chain reaction.

To identify biomarkers for chronic repetitive TBI, we performed global miRNA expression profiles from serum samples from control and TBI groups using TLDA platform. After the statistical analysis and correction for multiple comparisons, researchers identified a set of five and four miRNAs in group 2 (Service members with one or two incidences of TBI) and group 3 (Service members with three or more incidences of TBI), respectively. In both groups, miR-383 was identified as the only central nervous system specific miRNA detected. The other miRNAs that were identified are not central nervous system specific, and hence miR-383 is considered as a potential biomarker for chronic repetitive TBI. The researchers are performing the clinical correlation analysis to identify potential correlations with this miRNA. The published and unpublished preliminary data along with supporting evidence in literature suggest that miR-383 plays an important role in the pathology of mild TBI. In addition, peroxisome proliferator-activated receptor-γ and peroxiredoxin 3 are the main targets of miR-383 are important mediators of secondary neuronal injury. Future studies will be planned to study the role of miR-383 in response to acute blast exposure and also in long-term TBI outcome and to evaluate it as a potential therapeutic target for TBI.

This project was sponsored by Combat Casualty Care Research Program, Joint Program Committee-6.

Analytical Methods to Determine Urinary Metabolites for the Non-Invasive Assessment of Traumatic Brain Injury

Researchers at Missouri University of Science and Technology (Rolla, Missouri) and Phelps Health (Rolla, Missouri) are working in coordination with Fort Leonard Wood to develop and evaluate novel biomarker profiles using urinary metabolites to assess and characterize TBI. The comprehensive metabolic biomarker panel is based on the complex cascade of pathophysiological changes that accompany TBIs, including metabolites related to ionic flux, indiscriminate excitatory neurotransmitter release, increased glycolysis, and oxidative stress. This work ultimately aims toward the development of high-throughput assays for the non-invasive assessment of TBIs to aid with detection, prognosis, and more accurate prediction of return to duty using measurable metabolic changes.

Analytical methods development and applications: The research team developed and validated five analytical methods using high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS). One method is capable of simultaneously determining eight key metabolites in urine, including glutamic acid, homovanillic acid, 5-hydroxyindoleacetic acid, methionine sulfoxide, lactic acid, pyruvic acid, N-acetylaspartic acid, and F2-isoprostane without intensive sample preparation or preconcentration (Sigler et al., 2020). Another method for the analysis of thiols, including methionine, methionine sulfoxide, homocysteine, hoocystine, cysteine, cystine, glutathione, glutathione disulfide,

Photo credit: Michael Wilson/U.S. Navy

N-acetylcysteine, cysteinyl-glycine, and y-glutamyl-cysteine, and its application in blast exposure urine samples is being prepared for publication. Urine samples were collected from the Fort Leonard Wood Urban Mobility Breacher Course. In addition, we have developed separate methods for oxidative stress markers, such as lineolic acid and arachidonic acid, as well as validating enzyme-linked immunosorbent assays (ELISA) for the putative protein biomarkers S100B, glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1).

Biomarker panel profiling of pre- and post-blast exposure: These analytical methods have been deployed in a clinical study conducted at the Fort Leonard Wood Urban Mobility Breacher Course. Our biomarker panel was evaluated in 27 Service members throughout their course training to determine metabolic changes following low-level repeat blast exposures. In total, six urine samples and two blood samples were collected from each individual throughout the course, allowing for comparisons of pre- and post-blast exposures as well as correlations between urinary and serum metabolite levels at different time points. Several metabolites were found to be significantly altered throughout training, and detailed findings from the study will soon be published.

Case-control clinical study: The research team is conducting another clinical study at the General Leonard Wood Army Community Hospital. In this study, the research team plans to measure the urinary and serum metabolites in 60 TBI patient cases and 60 matched controls to determine metabolic changes in clinically confirmed TBIs. The detailed findings from this study are expected to be published early next year.

This research was sponsored by the Leonard Wood Institute in cooperation with the U.S. Army Research Laboratory and was accomplished under Cooperative Agreement Number W911NF-142-0034.

Early Stage Detection and Long-Term Monitoring of Subclinical and Clinical Traumatic Brain Injury

U.S. Department of Defense statistics indicate that in a majority of TBI cases vision is impaired. For example, in 2009 researchers reported a broad range and high incidence rates of visual complaints for patients in the Palo Alto Polytrauma Rehabilitation Center and Polytrauma Network Site outpatient clinics (Cockerham et al., 2009).

Currently, both baseline assessment for TBI and diagnostics at time of and after TBI are time-consuming, invasive or both, resulting in the urgent clinical need for a straightforward yet accurate test for subclinical and clinical TBI. Such technologies would enable early and adequate intervention, as well as new therapy development, thereby increasing quality and reducing cost of health care by focusing only on patients that need care (personalized medicine) and being able to monitor therapy success or lack thereof to refocus therapy (outcomes-based medicine).

Researchers at the University of Missouri - Kansas City's Vision Research Center (Kansas City, Missouri), working with Fort Leonard Wood's General Leonard Wood Army Community Hospital coordinated by the Acute Effects of Neurotrauma Consortium (AENC), are modifying and repurposing diagnostic technology approved by the FDA to generate a device for early and quantifiable diagnosis of TBI. The work focuses on the clinical validation of functional and structural measures of vision to streamline and accelerate the diagnostic process towards clinical implementation of novel TBI diagnostics. The technology provides a registered overlay of measures of visual function and topographical maps of eye structures while tracking and compensating for eye movements to eliminate fixation as a confounding factor. This combined with normative datasets acquired by Vision Research Center scientists enables reproducible patient testing and a robust correlation of eye structure with function. As part of the study, the testing time was reduced by an order of magnitude and the need for medicated eye drops during the testing was eliminated, enhancing patient compliance and acceptance. In addition, novel software is under development integrating multiple parameters to further improve data quality, testing accuracy, and reproducibility and to shorten the time needed for reliable testing and data analysis.

This research was sponsored by the Leonard Wood Institute in cooperation with the U.S. Army Research Laboratory and was accomplished under Cooperative Agreement Number W911NF-142-0034.

Brain Imaging Markers of Impaired Clearance of Alzheimer's Markers in TBI in Soldiers in Training

Amyloid (Aβ) deposition in TBI suggests a link between trauma and the development of dementia. Amyloid is one of the critical pathological features in Alzheimer's disease. The recently discovered glymphatic system is critical to Aβ clearance in the brain. The project objective is to develop a unique multi-modal functional and structural imaging platform to address the unmet challenge of in vivo characterization of the glymphatic system and amyloid deposition in acute TBI. The research aims to determine whether there are early markers of risk for neuropsychological and cognitive decline after blast exposure.

Nine instructors in breacher training, exposed to regular blasts as part of training Service members to breach a building, were imaged before initiating training and again after training. The research team plans to image another nine individuals working/living at Fort Leonard Wood before and after participation in non-blast-exposed activities as a comparison control group. The project plans to evaluate brain glymphatic activity in vivo with magnetic resonance diffusion tensor imaging, and Aβ deposition by means of Amyloid positron emission tomography (PET). The project will correlate imaging metrics with blast exposure and neuropsychological testing.

The baseline and follow-up imaging sessions were completed with breacher instructors. No baseline amyloid deposits were observed at baseline PET in breacher instructors prior to the breacher course, and magnetic resonance imaging showed no morphological abnormality. Four of the nine amyloid PET images were read as positive by a blinded rater after the breacher course. The four participants with positive images had an average of 131 blast exposures, and the five participants who remained negative had an average of 28 blast exposures. This is a statistically significant difference.

This research was sponsored by the Leonard Wood Institute in cooperation with the U.S. Army Research Laboratory and was accomplished under Cooperative Agreement Number W911NF-142-0034.

Brain Hemorrhage Detector Modernization Program

The brain hemorrhage detector (BHD) modernization project will aid far-forward medical personnel in detecting brain hematomas (bleeds) that result from head trauma at the point of injury. The Infrascanner 2500, the lead candidate produced by InfraScan, Inc., is an FDA-cleared, accurate, and clinically effective assessment solution for TBI casualties in settings where timely triage and treatment decisions are critical. The device is indicated to assess patients for CT scans but should not serve as a substitute for these scans. Physicians trained to use the device, or those under the direction of such a physician, are the intended users.

The predecessor device, the Infrascanner 2000, is currently fielded to the U.S. Marine Corps Battalion Aid Stations (Authorized Medical Allowance List 635 & 636). The modernized 2500 model will be approximately 50 percent smaller and lighter, provide better battery life, and have an improved user interface. The solution is being considered for the Army and the joint force for combat causality care in the forward theater of operations.

This program is funded by the Defense Health Agency.

Novel Protein-Templated Fluorescent Metal Nanocluster Probes to Investigate Blast-Induced Blood-Brain-Barrier Permeability

Blast-induced TBI has been identified as a major cause of debilitating neurocognitive dysfunction in combat veterans from the Iraq and Afghanistan wars. Repeated low-level blast (rLLB) exposures are common among Service members during training for combat readiness. Recent reports suggest that rLLB cause long-term cognitive deficits. Blast exposures, either single at high intensity or multiple at low overpressures, have a propensity to cause cerebral vascular rupture leading to cerebral micro-bleeds and compromised blood-brain barrier (BBB) integrity, since shockwaves can either directly cause vascular shearing or indirectly promote a sudden blood surge to the brain. Both can disrupt brain vasculature. Current methodologies to assess the BBB permeability changes in preclinical models using dye extravasation and/or the use of fluorescent-tagged dextrans have limitations of being either biotoxic or having a relatively shorter half-life in blood circulation.

Researchers at Walter Reed Army Institution of Research (Silver Spring, Maryland) were awarded funding in collaboration with U.S. Army Research Laboratories to develop protein-templated nanoparticle cluster technology to identify BBB that can be advantageous to existing methods. The research team aims to synthesize and use highly stable protein-templated metal nanoclusters (gold and europium) to circumvent the limitations of biotoxicity and shorter half-life of classical Evans blue and fluorescent dextrans to assess the degree of BBB permeability. The main objective of this work is to synthesize in-house bio-templates of metal nanoclusters conjugated with proteins of different molecular weights and inject them into rats following exposure to single and multiple blasts at varying overpressures. BBB permeability changes will then be measured. The experimental work has been initiated and is underway. It is

expected that analysis of the presence of protein conjugated nanoclusters in different brain regions before and after blast exposure in Au/Eu-nanocluster administered rat models will provide qualitative and quantitative information on BBB permeation in rLLB and high-intensity blast injuries.

This study was funded by the U.S. Army Research Laboratories Cooperative Agreement Grant MIPR0011703388.BASIC WRAIR 448-2.

Cumulative Effects of Low-Level Repeated Blast Exposure on the Brain

Exposure to repeated low-level blast overpressure, as periodically experienced by military personnel in using heavy weapon systems and performing breaching activities in operational and training environments, can lead to deficits in behavior and cognition. National Defense Authorization Act for FY2019 and FY2020, Sections 734, 253, and 717, mandate the DOD to monitor and characterize the effects of blast overpressure in training and operational environments. To identify the cumulative effects of repeated blast exposure in a preclinical model, an advanced blast simulator was used to closely mimic "free-field" blast. Rats were exposed to blast using various parameters: intensity (4, 6.5, or 8.5 pounds per square inch [psi]), frequencies (1, 4, 14, or 30 consecutive days of a single daily blast), and orientation (with animal front- or side-facing to the blast source). At 24 hours after the final blast overpressure exposure, fresh brain tissue was collected and macro-dissected into distinct regions: cortex, frontal cortex, hippocampus, and cerebellum. Western blot was used to measure brain levels of glial fibrillary acidic protein (GFAP), TAR DNA binding protein (TDP)-43, and Piezo2.

The study found that the response of these proteins to blast exposure depends on exposure parameters such as intensity, frequency, and orientation, and different brain regions have differential responses to blast. Expression of GFAP, an astrocyte-specific marker used as a blood-based biomarker of TBI, is significantly altered in the cerebellum following multiple exposures. The directionality of this change depends on blast intensity and orientation. The neurodegenerative disease-associated protein TDP-43 was also differentially affected depending on the number of blast overpressure exposures and brain region. It is significantly decreased in the hippocampus after one exposure but significantly increased in the hippocampus and frontal cortex after multiple exposures of the same intensity. The mechanosensitive ion channel protein Piezo2 is significantly increased in the cortex following a single blast overpressure exposure but significantly decreased in the cortex following repeated exposures. Overall, our results show region-specific responses to varied blast intensity, frequency, and orientation. This work was published in Frontiers in Cellular Neuroscience (Heyburn et al., 2021).

This project was sponsored by the Defense Health Agency and Military Operational Medicine Research Program and managed by Joint Program Committee-5.

FDA-Cleared Laboratory Assay for TBI Point of Care

The U.S. Army Medical Materiel Development Activity (USAMMDA) Warfighter Brain Health (WBH) Project Management Office (PMO) manages the Analyzer, Traumatic Brain Injury (ATBI) product development effort and leads its Integrated Product Team (IPT). USAMMDA has partnered with Abbott, a leader in diagnostics development worldwide, since 2014. Through research started at the Walter Reed Army Institute of Research (WRAIR) and the advanced development acquisition strategy of the ATBI IPT, two potential biomarkers have been identified in individuals suspected to have a TBI: ubiquitin carboxy-terminal hydrolase (UCH-L1) and glial fibrillary acidic protein (GFAP).

The first increment of the ATBI benchtop, developed with industry partner Banyan

Biomarkers, was a completed pivotal trial of 2,000 TBI patients. It received FDA approval as the first-ever blood serum laboratory test which can help rule out the need for a computed tomography (CT) scan of the head within 12 hours of TBI. Banyan did not commercialize the benchtop assay as it is a large hardware system with multiple peripheral components, has a sample processing and assay run-time of five hours, and has logistical challenges for fielding to military units.

The goal is to transition the same biomarkers from the Banyan benchtop system onto a cartridge-based assay that runs on the field- deployable ATBI Point of Care i-STAT blood analyzer system device (Figure 7-6), delivering results of the ATBI test within minutes. Leftover frozen samples from the benchtop trial were transferred to Abbott for a bridging comparison study to deliver an initial incremental solution plasma assay on the i-STAT Alinity. The bridging validation study on i-STAT was completed, Abbott submitted a regulatory packet to the FDA in June 2020, and the i-STAT and TBI plasma test were cleared by the FDA in January 2021. The device and test were commercially available in September 2021. In parallel, Abbott also began enrollment, in July 2020, of the clinical trial for the whole blood point-of-care (POC) ATBI biomarker test with rapid turn-around time; the team anticipates trial completion in late FY23 and subsequent FDA clearance of the whole blood POC bio-marker test in FY24. In November 2021, the first Service member was tested with the assay in a clinical implementation and operational assessment (CIOA) of the i-STAT Alinity and TBI plasma test. As of Oct 31, 2022 over 120 Service members have been tested in the CIOA demonstrating the benefits of this capability.

FIGURE 7-6: Field-Deployable ATBI Point of Care i-STAT Alinity Blood Analyzer System Device

A blood-based biomarker laboratory test for TBI will greatly enhance the ability of the DOD to objectively assess Service members who have suffered a suspected TBI. The goal of initial implementation will be to assist with management of patients who have suspected TBI, with particular emphasis on implementation in areas where a Service member would otherwise require an evacuation from operational settings to obtain a CT scan of the head. The Laboratory Assay for TBI has the potential to reduce unnecessary evacuations, solely for head CT scans, by about 30 percent. Deployment of the initial operational capability (IOC) of 20 i-STAT Alinity systems is on schedule for 2QFY24.

This program is managed by the U.S. Army Medical Materiel Development Activity Warfighter Brain Health Project Management Office.

Conflict Kinetics Platform-Based Assessment of Blast Exposure Effects on Performance: Enhancing Military Relevance of Research

Investigators at the Naval Health Research Center are working to employ a standing research capability in engagement with blast exposure measurement. The researchers hope to address the identified gap of an outcome metric that more directly represents military task performance. A combination of cognitive marksmanship assessment data with performance metrics during close-quarter combat will be aligned and analyzed as a function of overpressure as measured by blast gauges. Individuals exposed to blast, heavy weapons, or both were evaluated pre- and

post-test on training; the evaluations measured objective and subjective changes in behavior and performance on a battery of cognitive drills delivered in a simulated tactical environment.

This work was funded by the Defense Health Agency 734 Workgroup-LOI5.

Provisional Patent Filing for Novel TBI Blood Biomarker

TBI causes significant neuronal degeneration, and currently there are no treatments targeting neuronal death after TBI. This research effort, led by researchers at the Western University of Health Sciences, has identified a molecular mechanism that is activated in the hours following TBI, which lasts for several days and is directly related to neuronal degeneration. This mechanism consists of the prolonged activation of the calcium-dependent protease, calpain-2. Studies indicate that a selective calpain-2 inhibitor could represent a new class of neuroprotective drug, which could be administered in the hours/days following TBI or concussion, and provide a significant degree of neuroprotection, thus saving lives and reducing the long-term consequences of TBI.

A provisional patent covering the identification of a novel blood biomarker that reflects brain levels of calpain-2 activation has been filed with the U.S. Patent and Trademark Office.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Noninvasive Techniques to Predict Acute Hypotensive Episodes

Blast trauma is a leading cause of mortality post-9/11. Early prediction of the acute hypotensive episode (AHE) in critically ill patients can improve outcomes from blast-related injury. Researchers at Dartmouth Hitchcock Medical Center used five classification methods to predict an AHE 30 minutes in advance with 91 percent recall and 68 percent precision, by applying machine algorithms to the Medical Information Mart for Intensive Care (MIMIC) III Physionet dataset, which contains more than 60,000 real-world intensive care unit records. This work emphasizes the importance of exploring more noninvasive technologies for AHE prediction, especially for improved detection in closed-wound blast injuries. This research was published in Mil Med (Sun et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Neuroimaging of mTBI and Related Multisensory Dysfunction

Researchers at the Vanderbilt University Medical Center conducted an exploratory study of joint structural connectivity and cortical surface changes associated with mild TBI (mTBI) and its chronic symptoms to identify sensitive, quantitative diagnostic tests of visual, auditory, and multisensory integration dysfunction in patients with complex TBI. The team examined 12 mTBI and 26 control subjects. The researchers extracted a set of 588 cortical surface metrics and a set of 4,753 structural connectivity metrics from cortical surface regions and diffusion-weighted magnetic resonance imaging in each subject. The team used principal component analysis (PCA) to reduce the dimensionality of each metric set. After applying independent component analysis (ICA) to each PCA space individually and together in a joint ICA approach, the team identified a stable, independent component across the connectivity-only and joint ICAs, which presented significant group differences in subject loadings ($p < 0.05$, corrected). Researchers also found that two mTBI symptoms (slowed thinking and forgetfulness) were significantly correlated ($p < 0.05$, corrected) with mTBI subject loadings in a surface-only ICA. In addition, these surface-only loadings captured

Photo credit: Lance Cpl. Brienna Tuck/U.S. Marine Corps

an increase in bilateral cortical thickness (Kerley et al, 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Leveraging Gene Expression in the Blood as a Prognostic Biomarker of Spinal Cord Injury Severity in the Acute Stage

The discovery of non-invasive blood-based biomarkers of spinal cord injury (SCI) severity has the potential to transform treatment and diagnosis early after injury in the acute stage, ultimately leading to faster decision-making that could improve recovery and save lives. Using changes in gene expression within blood cells as a predictive biomarker is particularly attractive, as blood is easy to collect and can be analyzed quickly, thus allowing for faster decision-making that can save lives and lead to better patient outcomes.

Patients admitted to the emergency department at the Zuckerberg San Francisco General Hospital and Trauma Center underwent decompression surgery and blood collection as part of their acute treatment. In examining the potential of a blood biomarker, the Transforming Research and Clinical Knowledge (TRACK)-SCI team identified 197 gene expression alterations discovered in the blood of individuals who suffered an SCI, as compared with healthy and trauma control participants (Kyritsis et al., 2021). Several of these genes predicted later injury severity (American Spinal Injury Association Impairment Scale score) with an overall accuracy of approximately 72 percent. Further refinement and use of this biomarker has the potential to transform and guide early treatment decisions for injured service members, including those who have suffered common blast injuries that can cause SCI.

Moreover, the TRACK-SCI team is freely sharing these results in a database that can be used to

guide future development of targeted therapeutics to improve functional recovery after SCI for both civilians and Service members.

This effort was supported by the Spinal Cord Injury Research Program with program interest from Combat Casualty Care Research Program/ Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Distinguishing Tinnitus and Hearing Loss

Tinnitus is strongly associated with blast injury, and 38 percent of those who served in the Iraq War are suffering from it (Mizutari 2019). Researchers at the University of California, San Francisco aim to utilize advanced neuroimaging techniques to better identify neurophysiological underpinnings of tinnitus that will aid in improved diagnostics and targeted treatments. In a recently published study, they used 3Tesla structural magnetic resonance imaging in four patient cohorts: tinnitus with moderate hearing loss, moderate hearing loss only, tinnitus with normal hearing, and normal hearing only. They describe and compare volumetric changes in the corona radiata, nucleus accumbens, caudate nucleus, and inferior fronto-occipital fasciculus across the four separate cohorts and identify changes in the nucleus accumbens and inferior fronto-occipital fasciculus as most critical for accounting for hearing loss and/ or tinnitus (Yousef et al., 2021).

This effort was supported by the Peer Reviewed Medical Research Program.

Repetitive Blast Exposure Produces White Matter Axon Damage

The potential effects of blast exposure on the brain health of military personnel have raised concerns and led to increased surveillance of blast exposures. Neuroimaging studies have reported white matter abnormalities in brains of Service members with a history of blast exposure. However, blast effects on white matter microstructure remain poorly understood. As a novel approach to screen for white matter effects, transgenic mice that express fluorescent reporters to sensitively detect axon damage and myelin remodeling were exposed to simulated repetitive blasts (one per day on five consecutive days).

Axons were visualized using *Thy1-YFP-16* reporter mice that express yellow fluorescent protein (YFP) in a broad spectrum of neurons (Figure 7-7). Swelling along damaged axons forms varicosities that fill with YFP. The frequency and size of axonal varicosities were significantly increased in the corpus callosum (CC) and cingulum at three days after the final blast exposure versus sham procedures. CC immunolabeling for reactive astrocyte and microglial markers was also significantly increased. *NG2CreER;mTmG* mice were given tamoxifen on days two and three after the final blast to induce fluorescent labeling of newly synthesized myelin membranes, indicating plasticity and/or repair. Myelin synthesis was not altered in the CC over the intervening four or eight weeks after repetitive blast exposure. These experiments show the advantages of transgenic reporter mice for analysis of white matter injury that detects subtle, diffuse axon damage and the dynamic nature of myelin sheaths. These results show that repetitive low-level blast exposures produce infrequent but significant axon damage

FIGURE 7-7: Broad, sensitive screening for axon damage in brain sections after repetitive blast exposure using *Thy1-YFP-16* mice.

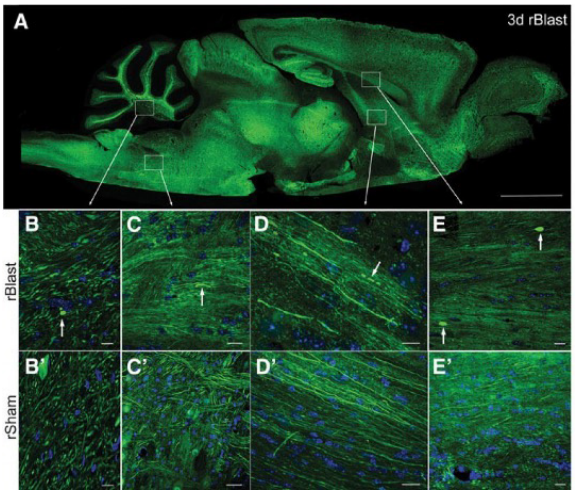


Photo credit: Graham Snodgrass/U.S. Army

along with neuroinflammation in white matter (Bradshaw et al., 2021a).

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine, DOD, and the Uniformed Services University through the UCSF–USUHS Partnership: Brain Injury and Disease Prevention, Treatment, and Research.

The Brain Expression of GFAP and Tau Following Blast Exposure in the Ferret

Blast exposures are a hallmark of contemporary military conflicts. Improved preclinical models of blast TBI for translation of pharmaceutical and therapeutic protocols. Compared with rodents, the ferret brain is larger, has substantial sulci, gyri, a higher white to gray matter ratio, and the hippocampus in a ventral position; these attributes facilitate comparison with the human brain. In a recent study, ferrets received compressed air shock waves and subsequent evaluation of glia and forms of tau following survival of up to 12 weeks.

Immunohistochemistry and western blot demonstrated altered distributions of astrogliosis and tau expression after blast exposure. Many aspects of the astrogliosis corresponded to human pathology: increased subpial reactivity, gliosis at gray white matter interfaces, and extensive outlining of blood vessels. Magnetic resonance imaging analysis showed numerous hypointensities occurring in the 12-week survival animals, appearing to correspond to luminal expansions of blood vessels. Changes in forms of tau, including phosphorylated tau, and the isoforms 3R and 4R were noted using immunohistochemistry and western blot in specific regions of the cerebral cortex. Of particular interest were the 3R and 4R isoforms, which modified their ratio after blast. The data strongly support the ferret as an animal model with highly translational features to study blast injury (Schwerin et al., 2021).

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine (CNRM-70- 8956), DOD and the Uniformed Services University through the UCSF–USUHS Partnership: Brain Injury and Disease Prevention, Treatment, and Research (PAT-74-3439), and the Psychological Health and Traumatic Brain Injury Research Program (W81XWH-13-2-0018), managed by the Congressionally Directed Medical Research Programs with programmatic oversight from the Combat Casualty Care Research Program/Joint Program Committee-6.

Preclinical Modeling for Translational Research – Ferret

The baseline behavior of ferrets in several common activities may serve as a reference for future intervention studies (Obasa, Schwerin, Ray, Strayhorn, & Juliano, 2022). Researchers reported that the ferret is the smallest mammal with a gyrencephalic cerebral cortex, which is important for studying neurological disorders in animal models. For optimal use of the ferrets, typical behavioral measurements are desirable. Researchers obtained a baseline level of behavior through a battery of tests assessing motor, social, memory, headache, and aspects of depressive-like behavior. Adult male ferrets participated in Open Field, Beam Walk, Sucrose Preference, Eye Contact, Light/Dark Box, Socialization, and Novel Object Recognition tests. Researchers assessed the ferrets in three age-related cohorts. Differences occurred between the youngest and older groups in several areas, suggesting that age may be important when evaluating ferret behavior. These experiments represent an important baseline of expected normative results that can provide a reference for normal ferret behavior and expected variability.

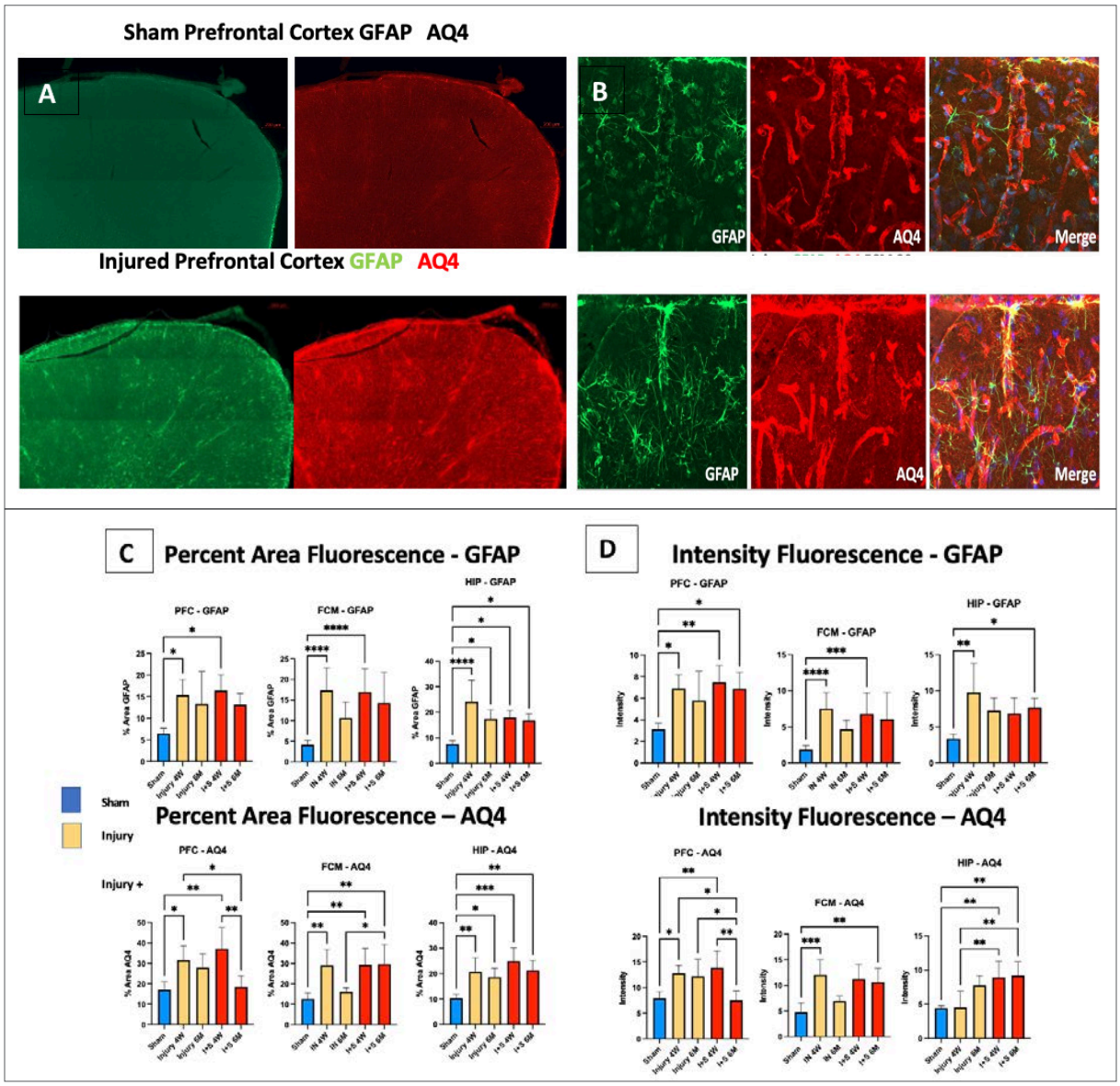
Current efforts involve sleep and related changes in astrocytic morphology, glial fibrillary acidic protein (GFAP) expression and aquaporin 4 (AQ4). A manuscript for publication is in production. Research showed that ferrets receiving an injury, specifically blast plus closed head injury model of engineered rotational acceleration, have more fractured sleep patterns than Sham animals. Over the past year, research showed that the patterns of activity obtained by the ferrets wearing actigraphs (closely related to sleep) significantly differed between injured or injured plus stress animals, compared with Sham animals. Measures of bouts of sleep vs activity showed injured and injured plus stressed animals revealed a more fractured sleep pattern than Sham animals.

This year, researchers added a vital component, showing that, in several neocortical regions and the hippocampus, expression of GFAP and AQ4 showed increases over time post injury. A subset of animals at four weeks post injury (WPI) and six months post injury (MPI) were evaluated immunohistochemically. Sections selected from the prefrontal cortex (PFC), medial frontal cortex (FCM), and a temporal location at the level of the hippocampus (HIP) were double labeled with chicken anti-GFAP and rabbit anti-AQ4. Optical image fluorescent stacks at 10x magnification were acquired to evaluate the GFAP and AQ4 reactivity; researchers assessed the fluorescent intensity and area of immunoreactivity. In each area of interest (PFC, FCM, & HIP), images were taken using the same exposure settings for each photo; red: 400ms, Green: 60ms, and Blue: 15ms, to avoid fully saturated pixels from skewing the analysis. Researchers obtained images using the tile and stitching (fuse) filter of nine tiles. Images were saved as TIF files and exported to Fiji software, converted to RGB color, and scaling was removed and set as pixels. The percent area labeled and fluorescent intensity was averaged and statistically compared between groups.

Figure 7-8 illustrates that the Sham animals show reduced intensity and area of immunoreactivity for GFAP and AQ4 in all areas imaged. Almost all imaged areas showed increases in both measurements at four WPI and six MPI; however, a few measurements did not show consistent increases at six MPI. This suggests that cortical areas showed variability in the persistence of inflammatory responses.

Researchers found that the usual colocalization of GFAP and AQ4 diminishes after injury. This lack of colocalization is remarkable because both markers are found in astrocytes; the AQ4 distributes preferentially in the astrocytic end feet and overlaps with the GFAP in the processes. After the injury, the AQ4 tends to lose polarization and appears more disorganized rather than adhering closely to blood vessels. The observation that GFAP (which normally occurs in astrocyte processes) and AQ4 lose colocalization and become less polarized after injury suggests that AQ4 may not function properly. This change to

FIGURE 7-8: **A** shows examples of ferret Prefrontal cortex immunoreactive for GFAP or AQ4 in Sham or injured animals. **B** shows higher power images of the same regions. **C** shows graphs of the percent area fluorescent in the Prefrontal Cortex for the Sham (blue), injured (yellow) or injured + stressed (red) at different survival times. **D** shows the same measurements for the intensity of fluorescence. There were statistically significant differences between groups as determined by a one-way ANOVA with Tukey's post hoc analysis for between groups *p < 0.05, **p < 0.01, ***p < 0.001, and ****p 0.0001

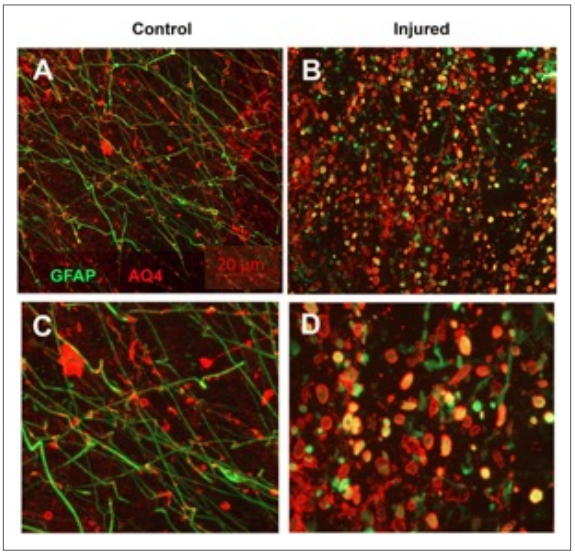


colocalization and polarization may contribute to the malfunction of the glymphatic system since AQ4 most likely plays a vital role in the absorption of interstitial and cellular fluid that contributes to the glymphatic absorption.

To evaluate findings of the ferret model, researchers began to assess the expression of GFAP and AQ4 in the human cortex in the prefrontal region of military personnel who received multiple blast injuries versus control subjects. Substantial distinctions were observed between these two groups. Fluorescent markers showed that the expression of GFAP in astrocytes was reduced in the subpial region. The intralaminar astrocytes showed distinctly altered morphology in the injured brains. With the control subjects, the intralaminar astrocytes had extensive smooth processes that

extended from layer one into layers two to three or deeper. The intralaminar astrocytes in the injured brains were no longer smooth and uninterrupted but broken into strings of bead-like structures. On closer evaluation with higher power views, the beaded intralaminar astrocytes were surrounded with AQ4 immunoreactivity, appearing somewhat like donuts (Figure 7-9). Findings suggest that AQ4 function changes after this injury and the associated altered morphology.

FIGURE 7-9: Intralaminar astrocytes at higher power showing the smooth and beaded configuration in the Control (A) and Injured (B). C and D are higher power showing rings of AQ4 immunoreactivity surrounding the GFAP beads.

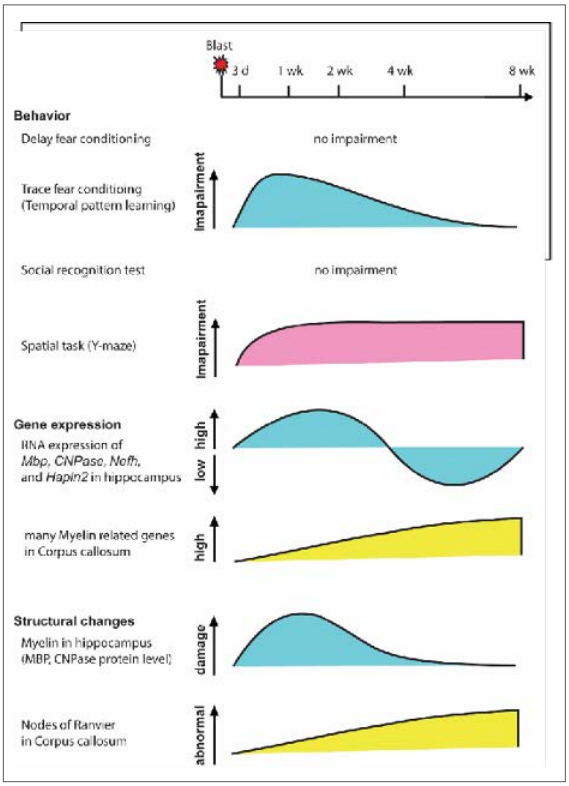


This research was supported by the CNRM-70-8956, Uniformed Services University (USU)-PAT-74-3439, and the Congressionally Directed Medical Research Programs W81XWH-13-2-0018.

Blast Exposure Altered Myelin-Related Genes and Proteins

In a collaborative project with the Uniformed Services University of the Health Sciences (USUHS) and National Institute on Alcohol Abuse and Alcoholism (NIAAA), investigators recently completed an extensive Center for Neuroscience and Regenerative Medicine (CNRM) supported project of the responses of myelin-related mRNA transcripts and proteins following single and repeated blast exposure using the USUHS Advanced Blast Simulator (Figure 7-10) (Nonaka et al., 2021). Quantitative polymerase chain reaction indicated there was a group of myelin and glial-related transcript in the hippocampus that were changed, as well as axonal node transcripts within the fear circuitry, including the medial prefrontal cortex and basolateral amygdala, and in two myelin rich areas: the corpus callosum and anterior commissure. The expression of 11 genes was examined at one, two, four, or eight weeks after a single blast exposure. In the hippocampus, transcripts associated with myelination, *Mbp* and *CNPase*, were altered, and two genes associated with axonal/nodes of Ranvier structure, neurofilament heavy chain (*Nefh*) and hyaluronan and proteoglycan link protein 2 (*Hapln2*, also known as *Bral1*). All four genes were downregulated at two to four weeks, but not at one or eight weeks, post-blast in the hippocampus. A different pattern was observed in the samples of the corpus callosum. At eight weeks after blast, all of the aforementioned myelin-related transcripts were elevated, as well as the proteoglycans, versican (*VCAN*), agrin, tenascin-R (*TNR*), neural/glial antigen 2 (*Ng2*), and G protein-coupled receptor 17 (*GPR17*); a sensor of brain injury, and Oligodendrocyte Transcription Factor 2 (*Olig2*); a transcription factor required for oligodendrocyte specification. In the corpus callosum, expression analysis revealed blast-related changes for, *Hapln2* and *Nefh*, two genes associated with the structure of the nodes of Ranvier. The nodes of Ranvier were evaluated for the paranodal marker, contactin-associated protein, Caspr, and the nodal gap marker, Nav1.6. In mice exposed to repeated blast, nodal gap length in the corpus callosum was significantly longer one and eight weeks after repeated blast. There was also an alteration in mRNA levels of glial, extracellular matrix and myelin-related genes in the corpus callosum after blast, where at eight weeks after exposure, all 12 of the sampled transcripts were elevated in blast mice compared to sham controls, with 11 of the 12 transcripts exhibiting increases greater than 20

FIGURE 7-10: Summary of time-dependent behavior, gene expression analysis, and structural analysis (protein and morphological) after blast. Trace fear abnormalities paralleled the time course of myelin structural changes after single and repeated blast, while spatial novelty preference deficits and structural change in the nodes of Ranvier and corpus callosum axons were evident only after repeated blast.



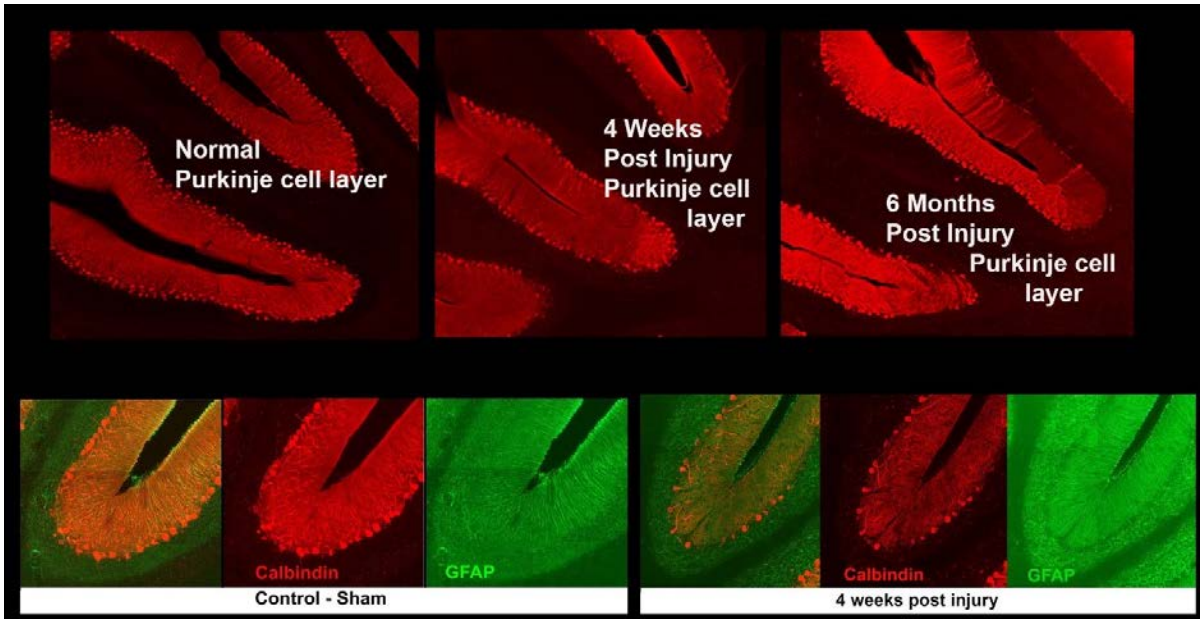
percent. A summary of their measures suggested complex changes follow blast exposure, including an alteration in trace fear conditioning (but not delayed conditioning), long-term impairment of spatial memory, alternation changes in transcription, and longer lasting shifts in myelin and node of Ranvier gene expression that may impair neurotransmission.

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA; Rockville, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine (306136-16.01- 6085a5), NIAAA Intramural Research Program, Uehara Memorial Foundation and Japan Society for Promotion of Science, University of Nebraska Medical Center's Electron Microscopy Core Facility, Nebraska Research Initiative, University of Nebraska Foundation, and Office of the Vice-Chancellor for Research.

The Impact of Blast and Rotation on the Ferret Cerebral Cortex and Cerebellum

Recent research shows substantial changes in the ferret cerebral cortex as a result of blast injury. As the smallest mammal with a gyrencephalic cerebral cortex, the ferret is an important animal model to test the effects of blast injury. Researchers at the Uniformed Services University of the Health Sciences (USUHS) recently published an article in the Journal of Neuropathology and Experimental Neurology showing that after blast injury, the ferret demonstrates dramatic increases in astrocytic reactivity, along with changes in levels of phosphorylated tau and isoforms of tau, which mimic the types of alterations seen in humans after blast and those with neurodegenerative diseases (Figure 7-11) (Schwerin et al., 2021). The study also found that using a combination injury, including blast plus a severe rotation, results in long-term behavioral deficits, as well as long-term alterations in markers similar to those seen after a blast injury. They tend to appear more quickly and persist for a relatively long time. Sleep also appears to show substantial deficits after the combination injury. Additionally, the study found, using the combination injury, that the cerebellum shows substantial evidence of damage. Although the cerebellum is critical to normal function, it is understudied after TBI. The cerebellum is intimately involved in both cognitive and motor function. Animals surviving for six months showed substantial pathology, including severe reduction of calbindin expression and limited ability to visualize Purkinje cells and their dendrites. Including stress in the injury paradigm resulted in pathology that included a strong reduction of calbindin expression in entire folia, incorporating Purkinje cells and their dendrites. In other regions, visibility of Purkinje cells was intermittent and occurred in a striped pattern suggesting that zebrin-related units

FIGURE 7-11: Top: Examples of cerebelli immunoreacted for Purkinje cells (Calbindin) at different times post-combined injury. Bottom: Cerebelli immunoreacted to reveal Purkinje cells (Calbindin) or Bergmann glia (GFAP) for control or four weeks post-injury. The Purkinje cell layer is highly disrupted post-injury, while the Bergmann glia are less affected.



were reduced in function. The Bergmann glia appeared relatively normal and well oriented, and in most instances maintained protective nests surrounding presumptive Purkinje cells.

The animals that survived for four weeks post-injury also showed pathology, but it was limited to restricted spotty regions throughout the posterior lobe. Several folia exhibited a striped pattern of calbindin immunoreactivity from the Purkinje cell dendrites, again suggesting that functional cerebellar units were impacted. Glial fibrillary acidic protein (GFAP)+ reactive astrocytes were observed in the granular layer and also surrounding Purkinje cells. Although the injured ferrets did not display obvious motor deficits associated with cerebellar problems, they collectively showed reductions in open field activities, decreased movements in the light-dark box, and decreased ability to maintain eye contact. The injured animals also showed impaired novel object recognition and socialization tests. These findings reveal chronic neuropathology in the cerebellum after a combination TBI accompanied by behavioral deficits associated more with cognition and memory than motor activity. It is essential that future studies further analyze and define the cerebellar pathology after blast plus rotational injury, since the cerebellum is becoming more and more recognized as a part of the brain that is essential to multiple functions, including sleep regulation, which is also affected by this injury.

This study was supported by the Center for Neuroscience and Regenerative Medicine (CNRM-70-8956, USU-PAT-74-3439), and the Psychological Health and Traumatic Brain Injury Research Program (W81XWH-13-2-0018), managed by the Congressionally Directed Medical Research Programs with programmatic oversight from the Combat Casualty Care Research Program/Joint Program Committee-6.

Genetic Deletion of Sterile Alpha and Toll/ Interleukin-1 Receptor Motif- Containing 1 (SARM-1) Ameliorates Axon Degeneration after Closed-Head Impact Injury

Following axonal perturbation, sterile alpha and TIR motif containing 1 (SARM-1) protein is activated and released from axons and depletes nicotinamide adenine dinucleotide (NAD+). NAD+ depletion leads to ionic imbalance and the breakdown of axons. Researchers employed SARM-1 knockout mice and wild type mice to determine SARM-1's role in corpus callosum axonal degeneration following a closed-head impact (Bradshaw et al., 2021b). As expected from previous work, impact resulted in corpus callosum atrophy, assessed by magnetic resonance imaging, that was significantly attenuated in the SARM-1 knockout animals. While magnetic resonance diffusion tensor imaging indicated there was a reduction in fractional anisotropy in both mouse strains, the SARM-1 deletion was higher in SARM-1 knockout mice. Immunostaining (Figure 7-12) likewise demonstrated atrophy in the corpus callosum after injury that was less in the mice lacking SARM-1.

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine and the DOD and the Uniformed Services University through the UCSF–USUHS Partnership: Brain Injury and Disease Prevention, Treatment, and Research.

FIGURE 7-12: Immunostaining (shown below) likewise demonstrated atrophy in the corpus callosum after injury that was less in the mice lacking SARM-1.

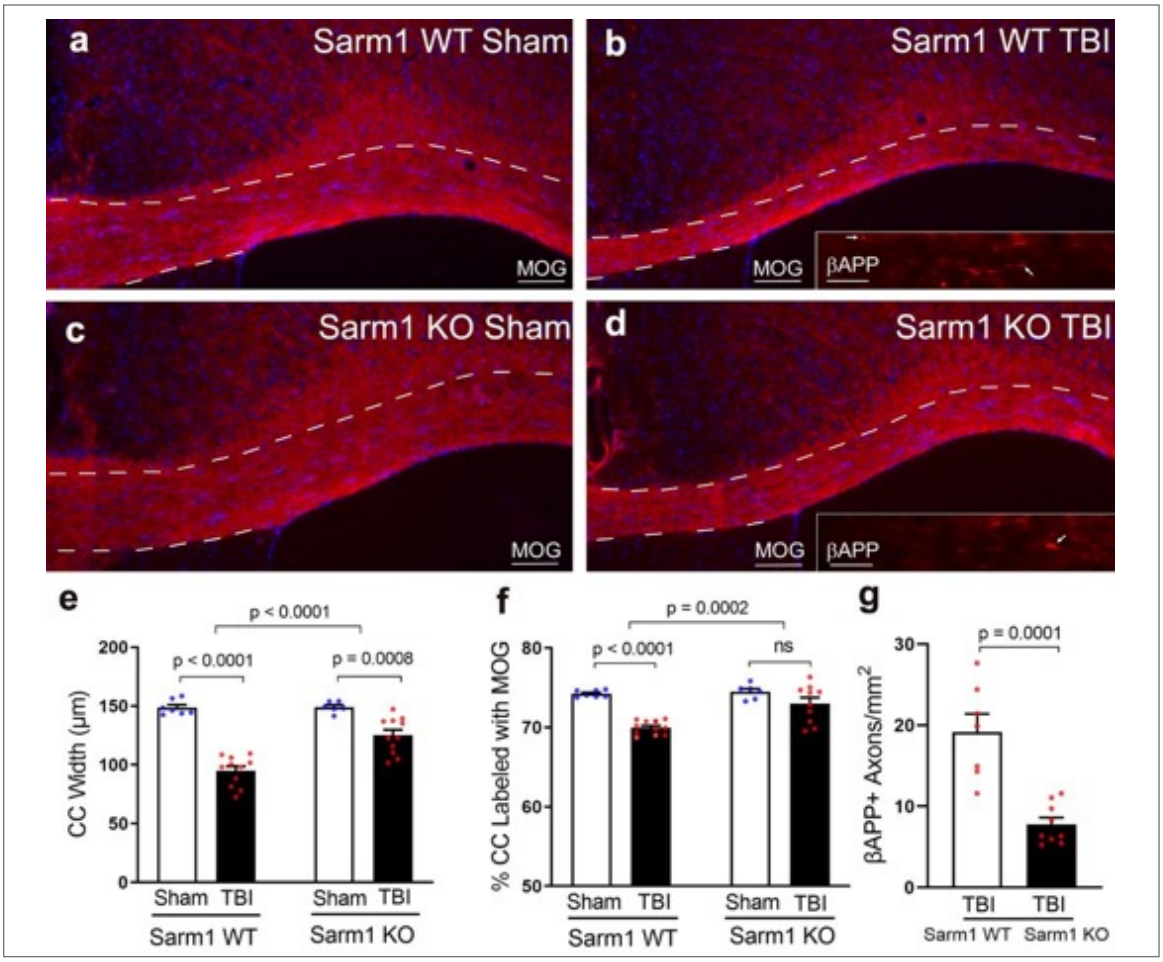


Photo credit: Staff Sgt. Thomas Calvert/U.S. Army

Imaging [18F]PI-2620 and Florbetaben F18 in Military Service Members with Blast-Related Mild Traumatic Brain Injury

TBI is recognized as one of the key injuries sustained by military personnel in the recent conflicts in Iraq and Afghanistan as well as during training. TBI has an acute impact on neurologic function; however, the potential long-term effects of TBI are poorly understood. mTBI, which generally results from multiple mild head injuries such as concussions and blast exposure from improvised explosive devices (IEDs), is associated with the development of a tauopathy referred to as chronic traumatic encephalopathy (CTE).

This study aims to determine how brain structure and cognitive function are affected by blast-related mild TBI (mTBI). Specifically, the study will 1) explore the presence and regional distribution of novel tau positron emission tomography (PET) and amyloid PET tracers in active-duty Service members with blast-related mTBI; 2) explore the impact of blast exposure on brain structure and function using multiple magnetic resonance imaging (MRI) modalities; and 3) characterize the neurocognitive deficits present in active-duty Service members with blast-related mTBI and correlate with PET and MRI.

The goal of this interdisciplinary proposal is to determine the relationship between mTBI and chronic neurodegeneration in active-duty Service members with a history of blast-related mTBIs and examine their risk for developing neurodegenerative disorders such as CTE. The performance site is the National Intrepid Center of Excellence (NICoE) at Walter Reed National Military Medical Center in Bethesda, Maryland.

For this study, the target enrollment is 30 subjects with a blast-related mTBI group (n = 20) and a healthy control group (n = 10).

We plan to use neuropsychological testing in conjunction with existing, emerging, and experimental imaging technologies to identify the most promising methods for detecting changes in brain structure and/or function that are attributable to mTBI. Specifically, we will perform two different positron emission tomography (PET) scans, one that identifies tau deposits and one that identifies amyloid beta deposits. We will also utilize structural and functional PET and administer a battery of neuropsychological tests that assess various behavioral and memory functions. All of these measures together will be used to assess possible brain pathology associated with blast-associated mTBI. Controls who have a history of combat deployment and mTBIs with no blast exposure and who are Defense Enrollment Eligibility Reporting System (DEERS) eligible will also be recruited. This study will be one of the first to use PET imaging to investigate tau and amyloid in active-duty Service members with a history of blast exposure to determine whether these individuals are at risk for developing CTE. The results from this proposal will aid in the delineation of the cognitive and neurobiological profile of blast-related mTBI in the military population; provide currently unavailable and crucial information regarding the risk for developing CTE-like dementia; and aid in the development of the adequate intervention, new treatments, and improved long-term care planning. Furthermore, the findings from this study may advance scientific knowledge about the neurobiological underpinnings of the complex interaction of mTBI and concomitant cognitive and functional deficits that can develop with age.

Clinical research at the NICoE was halted for much of 2020 and 2021 due to COVID-19 restrictions. However, the recent reportable outcomes include the submission of the Research Resumption Memo to NICoE leadership on 3 June 2021, the research roundtable presentation at NICoE on 17 June 2021, and five subjects enrolled in the study.

Neuroradiological Neuropathological Correlations

The Neuropathology-Neuroradiology Integration Core represents a novel union of two complementary but distinct laboratories and fields: Researchers from Uniformed Services University of the Health Sciences (USUHS) and National Institutes of Health (NIH) teamed up to develop and test novel magnetic resonance imaging (MRI) methods that could potentially identify TBI-related structural abnormalities in vivo. Currently, these abnormalities can only be identified ex vivo using laborious neuropathological techniques. To date, there have not been any neuroradiological methods developed that can reliably, robustly, and reproducibly detect different forms of TBI tissue damage in vivo, ranging from mild TBI (mTBI) to blast TBI, but particularly the latter, owing to its critical importance to Service members. This interdisciplinary team is working to change the status quo.

MRI methods sensitive to TBI-related damage could improve diagnoses and patient prognosis assessment and could be used to refine inclusion criteria for clinical trials of candidate therapeutics. A limitation of current TBI clinical trials, especially those involving “concussive” or mTBI, is that the inclusion criteria are based on subjective rather than objective assessments.

The first step in establishing bidirectional information flow between these disciplines is to develop and test various MRI stains and contrasts using controlled and well-characterized injured tissue specimens. The team has been evaluating whether various novel MRI contrasts can non-invasively detect sequelae of tissue damage or injury that are clearly visible in neuropathology slides. They are also assessing the robustness and reproducibility of these MRI methods to

ensure their suitability for more routine use. To enhance the possibility of information flowing from radiology to pathology, the team is interested in developing whole brain radiological assessment methods to help guide the neuropathologists to find damage throughout the entire brain, which without this information would be like finding a needle in a haystack.

The second step in this collaborative enterprise is to robustly and reliably fuse MRI data with image volumes obtained from tissue slices within the same specimens. Generally, the team first scans the tissue using MRI, and then the tissue is sectioned and stained histologically. To improve the quality of this process, the neuroimaging and neuropathological data are carefully co-registered and correlated.

The third step is to try to discover one or more potential quantitative MRI biomarkers that can effectively detect and confirm sequelae of TBI damage found by neuropathological methods.

The team is pleased to report that this year, a novel MRI acquisition and analysis methodology has shown promise in identifying blunt trauma damage non-invasively. The goal is to try to migrate this approach, which works with fixed tissue, to see if it is possible to detect TBI in vivo in living subjects. The team recently has gained access to blast injury tissue and is developing MRI methods with the potential for detecting blast injury-induced gliosis or gliotic scarring at the gray-white matter interface, which appears to be a signature of this mechanism of injury.

An aspirational goal is to be able to translate this new knowledge from bench to bedside — to implement promising new neuroimaging methods on clinical MRI scanners to test them with normal control subjects and patients with suspected TBI to assess their clinical efficacy.

Resulting work from this enterprise includes *Frontiers in Physics* (Benjamini et al., 2021a), *Frontiers in Neuroscience* (Avram, Sarlls, & Basser, 2021), Brain: *A Journal of Neurology* (Benjamini et al., 2021b), NeuroImage (Banjamini et al., 2020), and *Scientific Reports* (Pas, Komlosh, Perl, Basser, & Benjamini, 2020).

This work was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant no. ZIAHD000266) and the Center for Neuroregenerative Medicine under the auspices of the Henry Jackson Foundation.

The INVestigating traIning assoCiated blasT pAthology (INVICTA) Study

The Defense Health Agency (DHA) provided funding for the start-up and first year of the five-year INVICTA study, initiated to address concerns about the acute, cumulative, and long-term impact of repeated subconcussive blast exposure (RSCBE) on the brain, with high explosives (e.g., breacher training) and heavy weapons training (HWT; e.g., high caliber rifles, shoulder fired weapons, artillery), particularly for Range Safety Officers (RSOs) who are exposed repeatedly over two-year tours of duty. INVICTA is a prospective observational study featuring a detailed baseline assessment of Special Operators (SOs) and RSOs before HWT, with serial assessments through three months for SOs and two years for RSOs. Assessments include a wide range of blood biomarkers, cognitive testing, and a series of novel measures of sensory, motor, and physiologic performance. We hypothesize that RSCBE will adversely alter blood biomarker levels, memory, and other measures. The specific aims of the study were to 1) employ multiple methods in parallel to serially measure serum levels of UCH-L1, GFAP, and other biomarkers in relation to weapon firing; and 2) serially measure Hopkins Verbal Learning Test (HVLT-R) performance at specified times in relation to weapon firing.

INVICTA measures the impact of RSCBE on brain function, including memory, gait, balance, oculomotor function, cerebral blood flow,

Photo credit: Seaman Luke Cunningham/U.S. Navy

neuroimaging, and biomarkers. The participant population included Naval Special Warfare trainees, SOs, and land warfare RSOs as they participate in HWT 300 total: 200 firing of live HWT rounds (100 RSOs, 100 SOs), 50 firing either training rounds or rocket-propelled grenades (training controls), and 50 Navy personnel without blast exposure (naïve controls). INVICTA collects data at baseline (prior to HWT) and then at 30 minutes; six, 24, and 72 hours; two weeks; and three months following HWT. (Controls are assessed at same time points.) RSOs are also assessed at nine and 18 months, with a repeat of all the acute and subacute time points after heavy weapons firing at 18 months. INVICTA utilizes a between-subject comparison between exposed and two control groups and the within-subject comparisons of post-exposure assessments versus baseline.

This study will foster a better understanding of RSCBE and its acute, sub-acute, and chronic brain impact. Dose-response analysis will provide new guidance on RSCBE. The study addresses requirements of Section 734 of the FY18 National Defense Authorization Act (NDAA), Public Law 115-91, and FY20 NDAA, Public Law 116-92, Sec 742.

Through November 2021, 76 participants have been enrolled. Significant decrements in performance have been identified in the minutes to hours after blast exposure in measures of short term memory (HVLT-R), gait (AccWalker), and tactile discrimination (Brain Gauge) in exposed SOs and RSOs but not in non-exposed controls.

This study was funded by the Defense Health Agency.

TBI Field Capabilities Program

The U.S. Army Medical Materiel Development Activity (USAMMDA) Warfighter Brain Health (WBH) Project Management Office (PMO) manages the TBI Field Capabilities (formerly known as Noninvasive Neuroassessment Device Program) product development efforts. It also leads its Integrated Product Team (IPT). This program will enable capabilities for far-forward field medical personnel to:

1. Non-invasively assess TBI severity to inform triage, evacuation, treatment, and return to duty decisions within Role 1 and Role 2 environments.
2. Non-invasively monitor TBI-relevant physiologic parameters for confirmed TBI injuries in prolonged field care and during evacuation.
3. Provide life-saving interventions to save the lives of severe TBI casualties.

This capability will produce materiel to address unmet field medical gaps and increase healthcare provider capability in large-scale combat operations and multi-domain operations when prolonged field care is expected without immediate evacuation opportunities.

The IPT has focused on developing the Concept of Employment for TBI Field Capabilities in the future fight. The IPT has identified the need to address the capability needs for TBI Field Assessment, TBI Field Monitoring, and TBI Field Treatment. The TBI Field Assessment materiel solution will objectively enable the detection of hemorrhage size, location, and type, as well as confirm brain swelling. This program is poised to achieve Milestone A before the end of FY23.

This program is managed by the USAMMDA WBH PMO.

Prolonged Field Care

The Uniformed Services University CNRM, in collaboration with experts from the Johns Hopkins University Applied Physics Laboratory, designed, developed, and bench-tested prototypes of two devices designed to provide field- based diagnosis and care of traumatic epidural or subdural hemorrhage in austere environments.
The first device is an ultralight intracranial hemorrhage detector that uses advanced infrared technology to localize life-threatening subdural and epidural hematomas without needing a computerized tomography scanner. The second is a fully self-contained, tight seal burr hole device intended to stabilize a patient well past the golden hour.

In FY22, CNRM plans to develop a first-ever sheep model of severe, life-threatening subdural hematoma (SDH). CNRM's SDH sheep model will be used to optimize performance and assess the accuracy and reliability of the two devices

Anatomical and Injury Models

Gyrencephalic (Ferret) and Lissencephalic (Rat) Blast Brain Pathology Comparison

The U.S. Department of Defense reports that approximately 400,000 Service members have sustained TBIs, and among these, about 83 percent are mild TBI. However, brain injury criteria that can be readily used to assess risk and set safety guidelines in known Service member blast environments is currently inadequate. Lack of scalability and translatability of data from small lissencephalic animal models to human injuries have prompted questions regarding the use of rodent models. In addition, recent post-mortem clinical pathological studies have shown brain gyri/sulci interfaces to be vulnerable to blast exposure. Despite the valuable insights gained from these rodent injury models, the fundamental structural differences between rodent and human

Photo credit: Staff Sgt. Ridge Shan/U.S. Air Force

brains have prompted a growing interest in the utilization of other species with neuroanatomical features more closely resembling human brains (e.g., gyrencephalic rather than lissencephalic, with greater white matter content). Swine, in particular, have been studied for this purpose; however, although swine are a gyrencephalic species, the thickness of the skull imposes a considerable confounding biomechanical deviation from humans for the study of blast-induced neurotrauma.

As part of identifying scalability and threshold blast overpressure for the onset of visible injury, researchers at Walter Reed Army Institute of Research (Silver Spring, Maryland) have assessed and compared injury responses of lissencephalic (rat) and gyrencephalic (ferret) animal models using blood-brain barrier (BBB) permeability change. Male Sprague Dawley rats and male ferrets were exposed to different blast overpressures (5-20 psi) in prone position using an advanced blast simulator. Animals were intravenously injected with Evans blue dye to assess the BBB permeability changes 24 hours post-blast. Ferrets exposed to blast overpressures (20 psi) displayed a significant compromise in BBB integrity as identified by extravasation of Evans blue into brain parenchyma, particularly in white matter structures and hippocampus, whereas such changes were negligible in brain structures from rats exposed to identical blast overpressures. Similar findings were observed in neurochemical analyses with magnetic resonance spectroscopy (MRS) up to six months following blast. Further analyses of BBB injury thresholds are currently underway. Overall, these studies suggest that gyrencephalic animal models have better translatability to human blast injuries than do lissencephalic models and are therefore better suited to identify injury thresholds. MRS studies were conducted in collaboration with University of Maryland, Baltimore.

This work was funded by the Military Operational Medicine Research Program Blast, Blunt, and Accelerative Injury portfolio.

Framework for Accurate Calculation of Human Body Blast Exposure in Heavy Weapons Training Scenarios

Investigators from CFD Research Corp, U.S. Army Medical Research and Development Command, and Walter Reed Army Institute of Research developed a comprehensive computational framework for simulating blast overpressure exposure during heavy weapons military training. The framework is designed as a tool for military medics to monitor and analyze Service member blast exposure. The framework also provides interactive tools for creating training scenes which may include the following: 1) human body models with protective armor, 2) multiple Service members, weapons, and surrounding structures, 3) weapon blast signature, and 4) calculation of blast loads on Service members. The end point is to predict spatially and temporally resolved blast overpressure for all exposed personnel in a training scene. The framework offers several advantages, including fast calculation of blast wave pressure loads on the entire human body and/or injury sensitive organs. This research was published in Military Medicine (Przekwas et al., 2021).

This effort was managed by the DOD Blast Injury Research Coordinating Office with support and programmatic oversight by the U.S. Army Medical Research and Development Command.

Analyses of Guideline-Based Traumatic Brain Injury Treatment

TBIs sustained by Service members result in high rates of mortality and debilitating complications. Excellence in Prehospital Care (EPIC), a study conducted by researchers at the University of Arizona, Tucson, is the first major interventional study to show significant outcome improvement from care rendered in the prehospital environment. This research evaluates a series of critical and potentially practice-changing questions regarding how the prehospital physiology and treatment of moderate and severe TBI influence mortality and morbidity. These analyses highlight the critical importance of providing guideline-based treatment immediately after injury and not delaying until after evacuation. Clearly, if optimal care is not rendered in the field during the "platinum 10 minutes," indelible damage will occur that cannot be recovered by subsequent, higher-level care, no matter how advanced or specialized. The new findings will have an important impact on society by 1) further elucidating the factors involved in improving outcomes, 2) helping to direct the specific care rendered to our Service members, and 3) advancing and improving future brain injury research.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by Combat Casualty Care Research Program/Joint Program Committee-6.

Reproducibility of Head Kinematics in Large Animal Models

Head kinematics have previously been used to predict TBI pathology in both human and animal models, design safety equipment, develop finite element models, and assess brain injury risk during recreational activities and motor vehicle crashes. Researchers from The Mind Research Network and U.S. Army Aeromedical Research Lab analyzed data from the use of a triaxial angular rate sensor, as well as a six- degree of freedom sensor, mounted to the skull of a large animal model, which resulted in a published manuscript on the reproducibility of the model. This allowed for full characterization of both head and machine kinematics experienced during accelerator systems exposures. Previous studies that utilized acceleration models to produce TBI in large animal species likely overestimated the head kinematics experienced during trauma scenarios. Specifically, the head kinematics results indicate that animals experience approximately half of the angular velocity over approximately double the amount of time as is produced by the accelerator machine. Current findings will have

large implications for future studies of TBI, with or without hemorrhagic shock, in terms of model development.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Development of a 3D Phantom Leg Model for Thermal Testing

Acute limb ischemia can occur when blood flow to an extremity is interrupted by trauma, such as blast injury, resulting in severe blood loss requiring tourniquet application. Prolonged interruption of blood flow from ischemia or tourniquet use can result in nerve and muscle damage, permanent disability, and ultimately amputation. This project seeks to create a tourniquet that promotes therapeutic hypothermia via a limb-cooling sleeve and an insulating layer to decrease heat loss, with an air splint to immobilize the limb. Researchers at the University of California San Francisco and University of Washington, Harborview Medical Center have engineered a three-dimensional leg model to test cooling efficiency of the new tourniquet device before testing in human clinical studies. A patent application has been filed for the limb-cooling device. This research was published in the Proceedings of the 12th Global Virtual Conference on Applied Human Factors and Ergonomics (Mhetre, Shasheendra, Aarabi, Emery, & Germany, 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Non-Invasive Machine Learning Techniques to Predict Occult Hemorrhage

Ongoing hemorrhage often results from blast trauma, and thus far, there is no reliable method for non-invasively detecting and monitoring ongoing hemorrhage in closed wounds. The ability to do so would allow medical staff to better triage patients and resources. Researchers at Dartmouth-Hitchcock Medical Center are leveraging an optico-impedance system with machine learning algorithms to predict hemorrhage within the thorax, abdomen, and limb. They have used this device in one of the largest porcine hemorrhage studies to date (n = 60) and accurately detected a 2–3 percent blood volume loss 85 percent of the time. Preliminary results from a lower body negative pressure (LBNP) study in humans (n = 11) show a 95 percent accuracy in detecting 15-mmHg pressure changes. These findings demonstrate a viable solution for predicting deterioration in patients with closed wound injuries commonly incurred from blast trauma. This research was published in the proceedings of SPIE BiOS (Elliott et at., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Model Development of Wound and Burn Trauma in a Chemical Environment and Assessment of Medical Interventions

Investigators at the U.S. Army Medical Research Institute of Chemical Defense have initiated a study to leverage cutting-edge tissue engineering technology and established porcine models to determine the effectiveness of therapeutics and decontamination products for treatment of combined trauma in a chemical environment. A 3D dermal tissue system will be utilized to evaluate therapeutics and decontamination products in both burn wound models and non-burn full-thickness skin wounds. Data analysis by comparative pathology and tissue imaging is ongoing. Animal

model and protocol validation are in progress. Preliminary experiments investigating the impact of agent exposure and chemical decontamination on burn and non-burn wound healing with three chemical agents have been completed. This effort has the potential to deliver both novel models and therapeutic methods and products for care of burn and chemical agent combined injuries for preparedness for future Multi-Domain Operations.

Funding support provided by the Combat Casualty Care Research Program.

Models of Chronic Blast-Induced TBI Using the Advanced Blast Simulator and Closed Head Impact Model of Engineered Rotational Acceleration

The Center for Neuroscience and Regenerative Medicine's (CNRM) Translational Research Division conducts preclinical TBI studies that closely mirror human clinical studies. This novel approach enhances the ability to translate preclinical treatments into successful future clinical trials that will improve outcomes for Service members with TBI.

The Translational Research Division conducts a variety of complex injury models that closely replicate military-related TBIs: a combination of blast exposure and/or impact and rotational forces with stress-inducing environmental stimuli. The Division also assesses symptomology that is analogous to those measured in human trials: disruptions in mood (e.g., depression, anxiety), sleep, pain/headache, attention, impulsivity, and cognition (e.g., memory).

Through the Uniformed Services University of the Health Sciences (USUHS) Preclinical Behavior and Models Core, CNRM investigators have access to state-of-the-science devices for brain injury studies, such as the Advanced Blast Simulator (ABS) and the Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA). There are a limited number of ABS machines in the U.S., and the facilities at USUHS for modeling TBI, assessing behavior in mice, rats and ferrets, and MRI and PET facilities make for a unique research environment. The ABS at USUHS is designed to conduct blast exposure studies in mice, rats, and ferrets and is the only research equipment capable of producing the proper blast wave forms to mimic a free field explosion in animal models under closely controlled conditions. The CHIMERA device imparts the rotational force that is commonly involved in military related TBI, including the tertiary effects of blast exposure, and falls, vehicular accidents, and impact injuries during training and deployments. USUHS has CHIMERA devices that are scaled for studies in mouse, rat, and ferret models. The Division uses the ABS and CHIMERA shortly after one another, along with environmental stressors, to create animal TBI models that better account for the complex exposures experienced by Service members.

CNRM funded investigators have developed two proof-of-concept complex, chronic models of blast TBI in mice and ferrets that can inform translation to humans by incorporation of the combination of blast exposure, impact and/or rotational force, and stressful stimuli analogous to the complex environment and TBI exposures experienced by Service members. The pathological features seen in these mice and ferret models reflect novel features seen in post-mortem TBI human cases. These two state-of-the-science paradigms are intended to act as an efficient pipeline that rapidly and effectively evaluates candidate interventions. These interventions will be designed to yield a decisive determination of the treatment's effect (i.e., success or failure) on the primary outcome measure and will build in secondary outcome measures to improve future studies and clinical translation.

This research was supported by the Center for Neuroscience and Regenerative Medicine and the Defense Health Agency.

Photo credit: Sgt. Micha Pierce/U.S. Marine Corps

Involvement of Inflammatory Pathways in Trauma and Hemorrhagic Shock

Blast trauma in post-9/11 combat casualties often results in hemorrhagic shock and is a leading cause of mortality. A final common pathway for severe circulatory shock, including trauma/hemorrhagic shock, is refractory vascular failure. This is due to the inability of vascular smooth muscle to respond to vasoconstrictors, such as phenylephrine. Toll-like receptor 4 activation, increased inflammation, and decreased alpha-1 adrenergic receptor response (receptors that control vascular tone) have also been described. In cases of trauma/hemorrhagic shock, researchers hypothesized that decreased bioavailability of adrenergic receptors due to Toll-like receptor 4 activation contributes to vascular failure. In a recent study, researchers at the University of California, San Diego induced trauma/hemorrhagic shock in Wistar rats. Resatorvid and resveratrol were used to inhibit Toll-like receptor 4. Plasma was collected by researchers, then smooth muscle cells were incubated with lipopolysaccharide or plasma. Dot-blot was used to screen inflammatory cytokines. Immunofluorescence imaging and Western blot analysis were used to measure Toll-like receptor 4 along with activation of nuclear factor κB and cellular localization of the alpha-1 adrenergic receptor. Toll-like receptor 4 was knocked out using clustered, regularly interspaced short palindromic repeats/Cas9, and calcium influx was recorded by the study team following phenylephrine stimulation.

Study results indicated that trauma/hemorrhagic shock caused a decreased response to phenylephrine, while inhibition of Toll-like receptor 4 resulted in improved blood pressure. In smooth muscle cells, the Toll-like receptor 4/nuclear factor κB pathway was activated by trauma/hemorrhagic shock plasma. In addition, when Toll-like receptor 4 and the alpha-1 adrenergic receptor were double labeled, these receptors were shown to be co-localized on the cell membrane, and Toll-like receptor 4 activation caused co-internalization of both receptors. In cells incubated with trauma/hemorrhagic shock plasma, calcium influx was impaired, but it was restored when Toll-like receptor 4 was inhibited. In experimental trauma/hemorrhagic shock, the study found that activation of the Toll-like receptor 4 desensitizes vascular smooth muscle cells to vasopressors by reducing the levels of membrane alpha-1 adrenergic receptor. The team concluded

that improved treatments and survival from blast/trauma injuries that involve significant blood-loss/shock may result from further research in these pathways. This research was published in Crit Care Explor. (Mazor et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Pharmaceutical Interventions

Development of Antioxidant Therapy and Oxidative Stress Biomarker Assay for Blast-Induced TBI in Rat Models

TBI has received greater attention in diagnosis but remains lacking in its treatment. After initial trauma, the brain experiences an imbalance in the ratio of reactive oxygen and nitrogen species and the depletion of endogenous antioxidants like glutathione (GSH) that shields cells from free radical-induced oxidative stress by transforming into its oxidized form of glutathione disulfide (GSSG). TBI is also characterized by an elevation of membrane lipid peroxidation by-products and oxidative-stress generated biomarkers such as F2a-isoprostane, malondialdehyde, 4-Hydroxynonenal, N-acetylaspartic acid (NAA), and 5-Hydroxyindoleacetic acid. Apart from monitoring the biomarker levels, the reduced GSH/GSSG ratio is a good indicator of the oxidative stress in cells post-TBI.

Antioxidant prodrug like N-acetylcysteine amide (NACA) is a GSH precursor and efficient in improving the GSH level in the cell. NACA also has comparatively higher permeability through blood-brain barrier and cell membrane. Therefore, NACA was evaluated in this study as a therapeutic agent for treating TBI-induced rat models. Mild to severe TBI was induced using explosive blast placed at different distances from the rats. Some of the rats were pretreated with daily oral administration of the antioxidant prodrug NACA for seven days pre-blast and continued for three days post-blast. The rats were sacrificed to collect the urine, blood, and brain samples for the analysis of oxidative stress biomarkers using a liquid chromatography-tandem mass spectrometry (LC-MS/MS).
The LC-MS/MS methods, developed in both positive and negative electrospray ionization modes, yielded excellent sensitivity, linearity, spike recovery, and reproducibility. Additional steps included the derivatization and addition of antioxidants to stabilize the analytes in the collected samples. Analyte levels in urine and plasma samples were normalized using creatinine and corresponding internal standards. The GSH/GSSG ratios were also evaluated for the efficacy of NACA in treating TBI in Service members.

This research was sponsored by the Leonard Wood Institute in cooperation with the U.S. Army Research Laboratory and was accomplished under Cooperative Agreement Number W911NF-142-0034.

Blast Exposure, Stress Hormones, and the Effect of Anti-inflammatory Drugs

Blast-induced TBI is implicated as a major cause of posttraumatic stress disorder (PTSD), and neuroinflammation is reported to play a major role in the development of acute and chronic PTSD. Plasma levels of stress-related hormones such as adrenocorticotropic hormone (ACTH) and cortisol have shown a positive correlation with the severity of PTSD in patients. Using a rat model of blast-induced TBI, researchers at Walter Reed Army Institute of Research are exploring the acute effects of blast exposure on ACTH and corticosterone (the most abundant steroid in rats synthesized in the adrenal cortex and induced by the pituitary hormone, ACTH). The research team is also exploring the effects of the steroid (buprenorphine) and non-steroid (meloxicam) anti-inflammatory drugs on these stress hormone levels after blast exposure. The preliminary results indicate that blast exposure causes an acute increase in ACTH and corticosterone levels

in the rat plasma. The rats treated with the anti-inflammatory medications one hour before blast exposure had ACTH and corticosterone levels significantly lower than both blast-exposed and sham control rats. Further studies are in progress to determine the post-blast exposure treatment effects of these drugs on the levels of stress hormones.

This study was supported by the Military Operational Medicine Research Program/Joint Program Committee-5.

Testing Multiple TBI Drug Candidates in Phase 2 Adaptive Clinical Trials

The Traumatic Brain Injury Drug Treatment Integrated Product Team (TBI-DT IPT) is partnered with the University of California San Francisco and Transforming Research and Clinical Knowledge for Traumatic Brain Injury Network (TRACK-TBI NET) to test multiple TBI drug candidates in Phase 2 adaptive clinical trials.

Photo credit: U.S. Army

Currently, there are no FDA approved drugs for the treatment of TBI. The mission of TBI-DT IPT is to deliver an FDA cleared drug to limit neurologic damage and/or slow progression of injury, decrease morbidity and mortality, and improve cognitive outcomes in Service members who have sustained a TBI.

Over 30 clinical trials for TBI drugs have failed despite decades of research by government and private industry drug sponsors. This has prompted a paradigm shift in the TBI-DT IPT acquisition strategy for TBI drug pipeline development toward risk reduction in Phase 2 clinical trials. Focused investment in Phase 2 trials will improve the quality and quantity of TBI drugs in the pipeline of development, fully characterize drug candidates prior to entering Phase 3 trials, and thereby de-risk further investment in continued development toward FDA regulatory clearance.

TRACK-TBI NET is an integrated group of TBI subject matter experts, clinicians, surgeons, academicians and Level 1 trauma center clinical trial sites with a demonstrated ability to recruit clinical studies of individuals with TBI. Adaptive trial design leverages the advancements made by the TBI Endpoints Development Initiative (TED Initiative) as well as TRACK-TBI Precision Medicine projects' extensive dataset. TRACK-TBI NET established a partnership with University of Rochester, Center for Health Technology (CHeT) as the key integrator across stakeholders. Additionally, the public-private-partnership with Abbott to use the recently FDA-approved laboratory assay for TBI blood biomarkers, a program also managed by the Warfighter Brain Health Project Management Office, will serve as a linchpin research tool for this first-ever adaptive trial for TBI drug development.

TRACK-TBI NET and TBI-DT IPT have selected atorvastatin, minocycline, and candesartan generic drugs, approved for indications other than TBI,

for initial testing in a moderate TBI population adaptive trial design. Additional candidate drugs will enter the trial if the initial selected drugs prove futile; however, drugs that are safe and show promising results will move forward for further testing and development. TRACK-TBI NET is currently in the protocol development; drug and placebo blinding and distribution planning; and alignment with FDA phase of the project; trial enrollment is anticipated to begin in late FY22.

Testing generic drugs that have shown promise in previous TBI clinical studies represents the lowest risk and fastest regulatory pathway for TBI drug development. Adaptive trials allow for higher throughput for testing candidate solutions on a standardized, multi-center, quality-controlled TRACK-TBI NET platform. This acquisition strategy offers the best chance for success in identifying drugs that may show promise for treatment in moderate TBI, helping a population with the potential for meaningful functional improvement return to duty, and sustain the fighting force.

This research was funded by the Defense Health Program, U.S. Army Medical Materiel Development Activity.

Development of a Safe, Affordable, Operationally Effective, and Suitable Drug to Treat Service Members with PSTD

Posttraumatic stress disorder (PTSD) is a debilitating condition that develops following exposure to a traumatic event or events, including blast injuries. Based on empirical evidence, PTSD impacts mortality, morbidity, self-reported medical symptoms, quality of life/physical functioning, heath-compromising behaviors, comorbid substance abuse, and employment. PTSD is of particular concern among U.S. combat Veterans due to its estimated lifetime prevalence of 6 percent to 31 percent. This is a two- to four-fold increase in prevalence over that of the U.S. general population. A 2008 RAND report estimated the two-year cost of treating the 1.6 million military personnel who have deployed since 2001 at $4.0–$6.2 billion. Despite the high prevalence and costs of PTSD, only two drugs are approved by the FDA for treating PTSD. Post-approval evaluations of these two drugs demonstrate less than 50 percent efficacy in treating PTSD, and these drugs often produce problematic side effects. The primary objective for the PTSD Drug Treatment (PTSD-DT) Program is to, as quickly and efficiently as possible, develop and acquire a safe, affordable, operationally effective, and suitable drug to treat PTSD. Development of a drug to treat PTSD could improve outcomes after a traumatic event, return individuals to work sooner, and reduce the cost burden for health care.

By the end of FY21, 220 participants from the Cincinnati Veterans Affairs Medical Center, Tripler Army Medical Center, and Walter Reed National Military Medical Center were enrolled in the PTSD-DT program's enabling study to validate two recently updated tools used to diagnose and assess the severity of PTSD symptoms. The results of the enabling study will inform how these tools can be used for the PTSD-DT program's Phase 2 Adaptive Platform Trial (APT) inclusion criteria and outcome measures. During FY21, design of the innovative Phase 2 APT that will simultaneously and sequentially evaluate more than one drug prototype for more than one PTSD subtype in active duty Service members and Veterans, was ongoing. In addition, initial drug selection was completed in FY21. The first three drugs that will be tested on the platform are fluoxetine, vilazadone, and daridorexant. Study start is expected in FY23.

This research is supported by the Defense Health Agency.

Evaluation of Potential Stem-Cell Therapies for Traumatic Brain Injury

Currently, there is no FDA-approved treatment for TBI beyond physical therapy. However, cellular replacement therapy is considered a potential restorative strategy to repair

and revitalize the damaged brain tissue and consequently improve neurological functions. Researchers at the University of Miami, Coral Gables submitted an abstract to the 2021 Military Health System Research Symposium (MHSRS) conference for a presentation titled "Assessment of Neural Stem Cell Transplantation for Treating Penetrating Traumatic Brain Injury in a Rat Model." This research aimed to evaluate potential neuroprotection and neuroplasticity of cellular replacement therapy NSI-566, an FDA-approved, fetal-derived, epigenetically expanded stem cell line.

Study results revealed that intracerebral targeted treatment with human neural stem cell NSI-566 failed to provide significant benefits on improving motor and cognitive functions, regardless of the transplant location. The lack of therapeutic effects of neural stem cell transplantation was unexpected and may preclude continued preclinical TBI research on this cell line. This research was submitted as an abstract for presentation at the Military Health System Research Symposium (Okada-Rising, Pedersen, Figiel, Huynh, & Shear, 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Potassium Channel Activator Reduces Tinnitus in Noise-Exposed Mice

Loud noise and blast exposure may lead to hearing loss and tinnitus. Depending on the severity, tinnitus can be very disruptive, and it is the highest military service-connected disability among Veterans. A basic understanding of mechanisms and potential treatments is currently being developed, but there is no cure for tinnitus. It is thought that tinnitus develops when a loss of auditory nerve input to the brain creates compensation in central brain regions, leading to hyperactivity and spontaneous signaling in the brain.

University of Pittsburgh researchers are studying potassium channel activity linked to tinnitus. They developed a compound, RL-81, that activates KCNQ2/3 potassium channels (Marinos et al., 2021). RL-81 does not affect hearing at baseline or after noise exposure; however, it may function to treat tinnitus. Using a mouse model of noise exposure to induce tinnitus, half of the mice received RL-81 treatment starting one week after noise exposure, and mice were assessed two weeks after noise exposure. A behavioral test for tinnitus revealed that RL-81 treatment reduced the percentage of mice showing signs of tinnitus, suggesting that RL-81 may be a potential treatment for tinnitus, even seven days after noise exposure. Further experiments are needed to assess RL-81 treatment in a blast-induced animal model of tinnitus. Toxicology data and further preclinical analysis are ongoing.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Cellular and Molecular Targets for Potential Treatment of Extremity Wounds

Cellular-based therapies have been successful in treatment of major extremity wounds. However, challenges in production, storage, and delivery in field settings have largely limited their use for treatment in combat and prolonged field scenarios. Rapid treatment of extremity wounds, from events such as blast exposure, is a critical need following immediate stabilization of injured personnel. Researchers at Augusta University are exploring extracellular vesicles (EVs) as stable stem-cell derived therapy in an animal model of limb recovery following ischemia-reperfusion injury. In addition, the team compared adipose-derived EVs against other ischemia-reperfusion injury attenuators such as hydrogen sulfide and a cyclosporine derivative, NIM-811. In vitro studies demonstrated that NIM-811 was as or more effective than lyophilized exosomes for

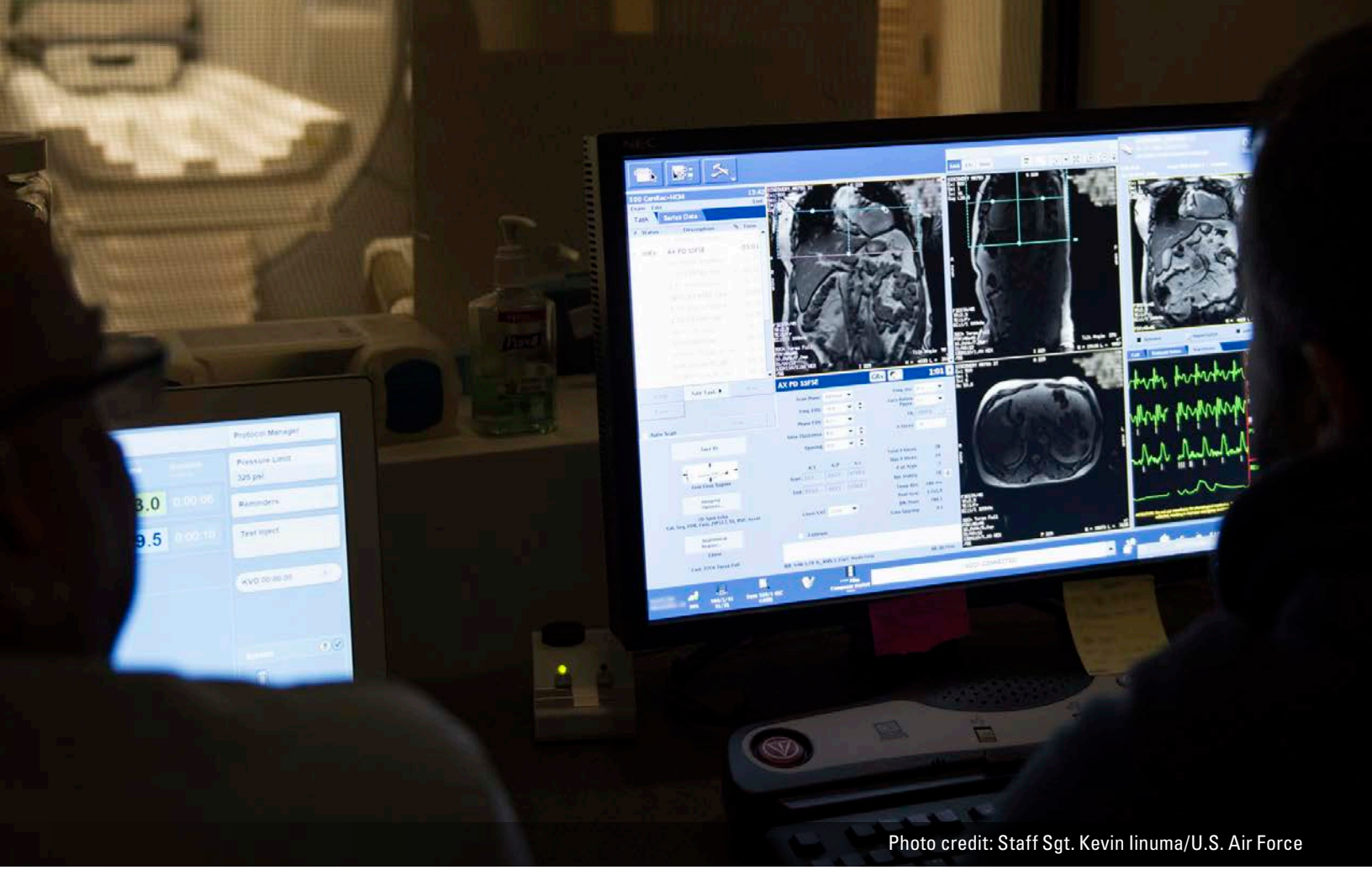


Photo credit: Staff Sgt. Kevin Iinuma/U.S. Air Force

preventing ischemia-reperfusion injury in tissue culture. These findings were confirmed in small animal studies. Additionally, NIM-811 was shown to have improved activity in reducing muscle inflammation, as measured by serum markers for inflammation, as well as oxidative stress following injury. Further studies are necessary to determine the utility of EVs and other injury attenuators for potential clinical use. Publications resulting from this work include Sci Rep. (El Baradie et al., 2021) and *Oxid Med Cell Longev.* (Kent, El Baradie, & Hamrick, 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Improved Cognition Post TBI with Metformin Treatment

Post-traumatic epilepsy is a recurrent seizure disorder due to brain trauma from sports, motor vehicle, and military-related incidents, which often include blast trauma. The resulting TBI alters synaptic plasticity, increases neuro-inflammation and neuronal death, and can ultimately lead to the seizure disorder even months to years after the fact. While there still are no effective TBI treatments, there are promising candidates for providing pleiotropic beneficial effects on these diverse cellular processes necessary for functional recovery.

Neurotrophins are known to be neuroprotective after injury; however, their short biological half-life and poor blood-brain barrier permeability have made it difficult to use neurotrophins in clinical settings. One promising strategy is to target downstream effectors of neurotrophins that can be manipulated pharmacologically. Researchers

at Rutgers University have identified two novel neurotrophic effectors: Ser/Thr kinase partitioning-defective 1 (Par1) and its downstream target RNA-binding protein Hu antigen D (HuD), which have been shown to be downregulated during early TBI, showing promise for potential posttraumatic epilepsy therapeutics (DiBona et al., 2021).

Their recent work focuses on treating central nervous system injuries with metformin, a diabetes medication, which seems to also have neuroprotective effects via the Par1/HuD pathways. Following TBI, metformin-treated animals demonstrated improved cognitive functioning as evidenced by improved spatial performance on the Morris Water Maze and increased nest-building which indicates improved emotional stability and well-being. In vitro analyses show that Metformin increased neuronal activation of Par1, known to play key roles in synaptic plasticity and neuro-inflammation. Microglia in metformin-treated injured animals exhibit increased ramified and decreased amoeboid morphology compared with vehicle controls, further suggesting metformin treatment reduces neuro-inflammation. These promising results with metformin provide evidence that treatment for TBI from blast injury or other mechanism may be able to prevent or acutely treat posttraumatic epilepsy sequelae.

This effort was supported by the Epilepsy Research Program.

FDA Submission for a Phase 2 Study to Evaluate Drug Product to Limit Burn Severity

A recent study aimed to advance a potential drug product, cP12, which is a fibronectin-derived peptide that has shown to limit burn injury progression and expedite wound closure in a relevant animal model of pig. The FDA accepted the applications for an Orphan Drug Designation, Fast Track Designation, and an Investigational New Drug. The first-in-human, phase 1 clinical trial was a randomized, double-blinded, placebo-controlled study assessing the safety, tolerability, and pharmacokinetic profile of single ascending intravenous doses of cP12 in healthy adult subjects of both sexes. Each subject was randomized to receive either a single dose of cP12 or placebo. Five cohorts of 40 subjects completed the study. The phase 1 results showed no adverse events other than the most common to include pruritus, feeling hot, headaches, and flushing that were experienced by 13 percent of the subjects at the higher doses. The FY21 accomplishment resulted in an FDA submission for a phase 2a clinical trial protocol using the human data collected in this award.

This effort was supported by the Military Burn Research Program with program interest from the Combat Casualty Care Research Program/Joint Program Committee-6.

Tranexamic Acid Reduced Burn Wound Progression in the Mouse Model

A recent study aims to demonstrate that intravenous administration of tranexamic acid (TXA) will reduce burn wound progression, cutaneous tissue, and organ edema in the animal model (Carter, 2021). Recent accomplishments of the study include completion of animal model study and demonstration of TXA efficacy in burn wound progression.

The investigators used a rat model with comb burn injury only with an adjacent 30 percent total body surface area burns, which resulted in full-thickness burns. The comb burn injury model resulted in interspaces that represented the ischemic zones and simulated the zone of stasis. Four experimental groups were studied: sham, burn with no treatment, burn with TXA given once post-injury, and burn with TXA given daily until sacrifice. Results were analyzed using histology and photographic evaluation of the ischemic zones. TXA administration showed benefits of having less evidence of necrosis visually and microscopically. The percentage of unburned interspaces

undergoing necrosis was significantly reduced in the treatment group when compared with untreated burn controls by photographic image analysis and by standard microscopy.

This effort was supported by the Military Burn Research Program with program interest from the Combat Casualty Care Research Program/Joint Program Committee-6.

Repurposing Drugs to Treat Acute Spinal Cord Injury

Although more than 17,500 individuals experience spinal cord injuries in the United States each year, acute therapeutics are lacking. Researchers at the University of Arizona are trying to change this by testing the efficacy of the drug formoterol to protect neurons and promote functional recovery after spinal cord injury. Formoterol works by increasing the number of functional mitochondria, which supply cells with the energy needed for normal function. Without treatment, initial trauma to the spinal cord may cause secondary injury, including mitochondrial dysfunction and death of initially uninjured neurons when damaged blood vessels no longer deliver oxygen effectively. Recent results are promising: both male and female mice given optimal doses of formoteral starting eight hours after injury experienced increased mitochondrial biogenesis, decreased lesion size, restored body weight and muscle mass, and increased locomotor recovery (Scholpa, Simmons, Crossman, & Schnellmann, 2019) (Scholpa, Simmons, Crossman, & Schnellmann, 2021). Because formoterol is already FDA-approved for the treatment of asthma and other lung conditions, translating this promising animal work to human clinical studies can occur more quickly and at a lower cost than with an entirely new drug. Formoterol, therefore, has a high potential to advance therapeutic treatment that can prevent secondary injury and improve function after spinal cord injury, benefiting Service members and civilians who experience spinal cord injury.

This effort was supported by the Spinal Cord Injury Research Program with program interest from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Small-Molecule Tropomycin-Related Kinase B Activator for Treatment of Blast-Induced Vision Loss and Damage

Blast pressure from TBI can damage the eye, often causing vision loss. Upon blast damage to the eyes' cells and nerves, these cells can start releasing factors that cause further inflammation, swelling, and cell death. Therefore, optimally, treatment for blast eye injuries would start as soon and as close to the battlefield and blast exposure as possible to mitigate this degeneration. It has been previously shown that activating tropomycin-related kinase B (TrkB) receptors within the eye can decrease blast-induced cell degeneration and cell death. However, one of the main TrkB activators, brain-derived neurotrophic facter (BDNF), cannot cross the blood-brain barrier to exert its protective effects in the eye. Therefore, to treat blast-damaged eye tissue, BDNF must be injected directly into the eye. This type of drug delivery is not practical or feasible on a battlefield or in an emergency medical vehicle. To address this problem, researchers at Emory University examined another TrkB activator which can cross the blood-brain and blood-retina barrier, small molecule N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-2-oxopiperidine-3-carboxamide (HIOC). The team hypothesized that activation of TrkB by systemic administration of HIOC could help protect against blast pressure-induced vision loss.

In an article published in the Journal of Neurotrauma (Dhakal et al, 2021), the researchers used a mouse ocular blast injury model to mimic the blast exposure of a Service member on the battlefield. Tests showed, upon blast exposure, that mice had decreased visual contrast sensitivity and acuity and their inner retinas were damaged. Immediately after blast

exposure, mice were systemically administered HIOC via an injection in the abdomen. Mice continued treatment with HIOC once a day for a week. Research demonstrated HIOC treatment helped protect against the blast-induced vision loss and retina damage. If mice were treated with a TrkB blocker before HIOC treatment, HIOC's blast protective effects were lost, confirming HIOC works via TrkB receptors. Results showed that HIOC blast treatment helped protect against mouse vision loss when first administered systemically up to three hours after ocular blast exposure. If initial treatment was delayed for 24 hours, HIOC's protective effects were lost. These results highlight the importance of finding therapeutics that can be easily administered in the field, as close to time of injury as possible. With HIOC's ability to activate TrkB receptors through systemic administration, the researchers have found a potential therapeutic approach to help preserve visual function after blast or other blunt force trauma to the eyes.

There is a provisional patent application in 2021 for TrkB activators and their use in treating and/or preventing vision loss.

This effort was supported by the Vision Research Program.

Cell Therapy Approaches to TBI

Cell therapeutic approaches to TBI treatment have received intense research interest, where the differentiation of cells with implantation has shown promise for establishment of new connections and the release of neurotrophic factors that promote repair. Researchers utilized human induced pluripotent stem cells (iPSCs) following a mild controlled cortical impact (Nieves et al., 2020b). Their goal was to determine the viability of implanted neural stem cells, neuroblasts, and astrocytes, as well as assessment of functional sensory motor effects.

Neural stem cells and neuroblasts were found to best tolerate implantation into the host cerebral cortex, and the grafts extended processes into the contralateral corpus callosum, with some ipsilateral extension into the external capsule to the entorhinal cortex. However, improvement of sensorimotor function and an assessment of cell implant numbers were inconsistent. Overall findings showed the implants matured to neuronal fates, supporting the feasibility of implantation technologies, but there was exacerbated neuronal loss in the region of the injury, as well as astrogliosis in female mice (but not males). Overall, results suggest it is technically feasible and iPSCs are viable, but the challenge of employment of a cross-species xenotransplantation may result in deleterious outcomes. Homologous patient specific stem cells may prove a more viable approach.

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine.

Transcriptomic Analysis of Candesartan Treatment after TBI

The application of transcriptomic analyses following TBI is a burgeoning field that demonstrates the body's complex response to injury as well as drug treatments. Researchers evaluated the alteration in brain transcripts following controlled cortical impact and treatment with a promising therapeutic, candesartan. This compound is an angiotensin receptor blocker that at low doses had been proven to reduce TBI neuropathology and improve functional recovery (Attilio et al., 2021). Transcriptomic profiling was performed in injured mice and in mice that received candesartan by the intraperitoneal route for three days, starting six hours after injury, or for 29 days by osmotic pump infusion. There was a dramatic change of differentially expressed genes at day three in the hippocampus that included the alteration of genes mediating angiogenesis, interferon signaling, extracellular matrix transcripts (e.g., integrins), and genes related to chromosome maintenance and DNA replication. Over time, many of the differences were decreased, but the groups of mice treated for 29 days indicated that candesartan treatment reduced the expression of transcripts that regulate inflammation. Interestingly, in uninjured (sham)

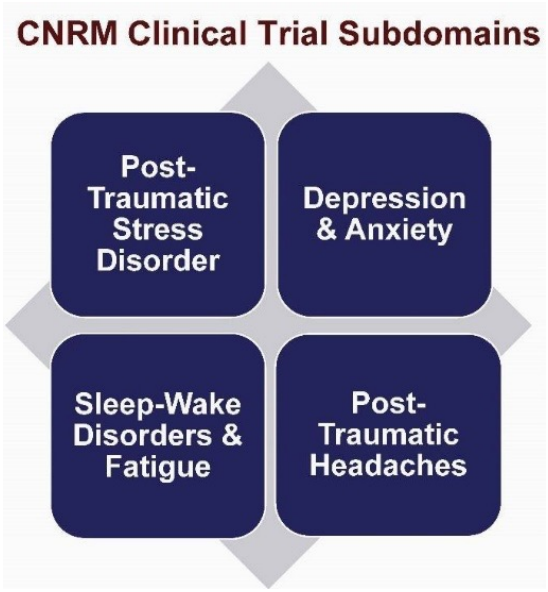
animals, 384 genes were differentially expressed by treatment with candesartan alone in the hippocampus, showing that candesartan was able to powerfully influence gene expression in the brain even without injury. The data show the complexity of gene expression changes after injury, with time and region dependent alterations in gene expression, and a differential response to candesartan treatment; the data also provide opportunities for further analysis (Figure 7-13).

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine (Grant no. G170244014) and the Tri-Service Nursing Research Program Grant no. TSN-75-N17-C03.

Center for Neuroscience and Regenerative Medicine Clinical Trials

The Center for Neuroscience and Regenerative Medicine (CNRM) clinical trials strategically address treatment gaps in TBI-related symptomatology, such as post-traumatic stress disorder, depression, insomnia, and headaches (Figure 7-14).

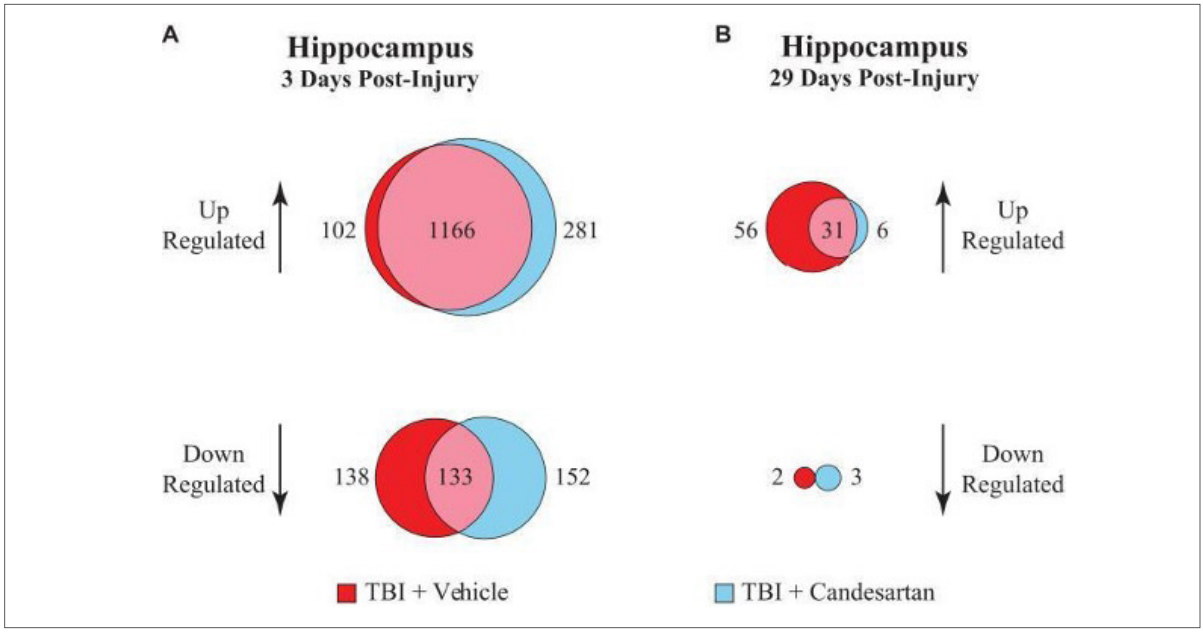
FIGURE 7-14: CNRM Clinical Trial Subdomains



Current treatment options for these symptoms are only moderately effective, which impacts the health, readiness, and competitive edge of our Nation's Armed Forces. The trials expand upon previous research to narrow knowledge gaps and improve TBI treatment guidelines.

The clinical trials apply novel pharmacologic (drug) and non-pharmacologic treatment approaches to a variety of symptoms across multiple

FIGURE 7-13: Unique gene analysis in the hippocampus at 3 and 29 days post-injury.



timespans (e.g., acute, sub-acute, and chronic). Exerting the most rigorous standards, the trials are multicenter, randomized, double-blinded, and placebo-controlled.

Leveraging the extensive partnerships of the Uniformed Services University of the Health Sciences (USUHS) outside the National Capital Region, CNRM's multicenter clinical trials will be conducted at several major military treatment facilities in the United States. Additional remote clinical trials will utilize USUHS' partnerships and a vast array of Defense Health Agency (DHA) and U.S. Department of Veterans Affairs treatment facilities. The studies involve some of the country's leading subject matter experts in TBI-related mood disorders, sleep disruptions, and headaches both within and outside of the DHA.

Surgical Interventions

The Impact of Direct Peritoneal Resuscitation on Survival of Combined Hemorrhage and Burn Injury

Wounded Service members commonly suffer from a combination of burn injury and hemorrhagic shock. Though we know little about the optimal strategy for addressing combined injury, current protocols for resuscitation are well defined for isolated burn injury and hemorrhagic shock. Survival after hemorrhagic shock has been shown to improve in rats with direct peritoneal resuscitation (DPR), but it is unclear what role this plays in survival of those with a combined burn/hemorrhage injury. Researchers at the University of Cincinnati hypothesized that DPR would improve survival in mice after combined burn injury and hemorrhage.

Mice were subjected to a 30 percent total body surface area scald in a 90°C water bath for seven seconds, followed by administration of DPR with either normal saline or peritoneal dialysis solution (Delflex). No peritoneal solution was administered to control mice. Both underwent a controlled hemorrhage shock to a systolic blood pressure of 25 mm Hg. They were resuscitated to a target blood pressure using either lactated Ringer's (LR) or a 1:1 ratio of fresh frozen plasma (FFP) and packed red blood cells (pRBCs). At 24 hours following injury, median survival time for mice with no DPR in combination with intravascular LR resuscitation was 1.47 hours, as opposed to 2.08 hours with pRBC:FFP. When intraperitoneal normal saline or Delflex was added, median survival time significantly improved. Mice that received DPR with LR, pRBC:FFP alone, and LR alone, required more intravascular volume than mice that received DPR followed by pRBC:FFP. Delflex was associated with lower levels of interleukin 10 and intestinal fatty acid binding protein and higher levels of tumor necrosis factor alpha and macrophage inflammatory protein one alpha. A reduced amount of lung injury was seen one-hour post-resuscitation with intraperitoneal normal saline but showed similar severity to Delflex at four hours.

Researchers concluded that DPR leads to increased survival in mice after a combined burn injury and hemorrhage event, and survival was similar with the use of normal saline or Delflex. DPR with normal saline delayed the progression of acute lung injury and reduced the inflammatory response seen with Delflex. Service members with combined burn injury and hemorrhage may benefit from treatment with DPR. This work was published in Military Medicine (Jung, et al., 2020).

This research was supported by the 711th Human Performance Wing through the U.S. Air Force Budget Activity 6.3.

Retrievable Stent Graft for Rapid Control of Non-Compressible Torso Hemorrhage

Researchers at The Ohio State University have developed a dumbbell-shaped (Rescue) stent that allows for vascular repair, especially in the hostile or actively hemorrhaging operative field. The Rescue stent has achieved remarkable success with control of hemorrhage in the cava as well as both the thoracic and abdominal aorta. The results

Photo credit: Pfc. Duke Edwards/U.S. Air Force

have revealed reduced blood loss, spinal cord ischemia, organ failure, and mortality. Recently, the Principal Investigator developed a dumbbell design that will offer not just hemorrhage control but also a space in which to repair the aorta while the stent is still in place. The laser cut prototypes have been as successful as anticipated. A prototype micro pressure sensor, only a few millimeters in size, has been developed and is beginning calibration. Final testing in vivo is underway.

Compared with aortic balloon occlusion, a Rescue stent offers superior hemorrhage control and survival by virtue of reduced ischemic injury and direct control of the hemorrhagic injury. The Rescue stent may become a useful tool for damage control, especially on the battlefield, where definitive repair presents logistical challenges. Publications resulting from this work include *J Biomed Mater Res B Appl Biomater* (Elsisy et al., 2020) and *J Trauma Acute Care Surg.* (Go et al., 2020).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Safety and Efficiency of Polymerized Human Hemoglobin Formulations as Potential Hemoglobin-Based Oxygen Carrier Therapies

Hemoglobin (Hb)-based O2 carriers (HBOCs) have been proposed as red blood cell (RBC) substitutes for use in transfusion medicine, such as is often necessary for blast injury. Polymerized human hemoglobin (PolyHb) constitutes the most realistic, scalable, and economical type of HBOC. The award published several findings (Muller et al., 2020a, 2020b; Williams et al., 2020a, 2020b) regarding the safety and efficiency of PolyhHb formulations, consisting of either a sterile injectable fluid or dry powder that can be reconstituted with water for injection for therapeutic use in hemorrhagic shock (HS)

resuscitation with and without TBI. These studies found that the molecular size of PolyHb determines vasoactivity, circulation time, mechanism of elimination, toxicity, and inflammation induced by its infusion. These studies further indicated that large molecular diameter PolybHb are as efficacious as fresh blood in restoring cardiac function, increasing O2 carrying capacity, and restoring hemodynamics and oxygen delivery without affecting O2 delivery or extraction by tissues in preclinical trauma models. As such, these results suggest that PolybHb are safe and could be an alternative to blood for resuscitation from HS with and without TBI when blood is not available or when the logistical constraints of refrigerated blood prevent access, assuming that additional testing demonstrates similar favorable results.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Prototype Testing of a Smart Oxygenation System in Human Volunteers

Researchers at the University of Texas, Medical Branch, Galveston have developed and been granted a patent for a Smart Oxygenation System (SOS) which is capable of assessing and providing early warnings of lung injury. The SOS device incorporates the Exspiron and the FreeO2 system in closed loop oxygen control mode, along with a pulse oximeter. The SOS allows for ventilatory parameters, primarily from Exspiron, and oxygenation parameters from the FreeO2 pulse oximeter + flow sensor. Detailed warning alerts and alarms are incorporated into the SOS software.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Development of Damage-Control Resuscitation Hemorrhage Helper Clinical Decision Support System

Although damage-control resuscitation (DCR) improves trauma survival, consistent adherence to DCR principles through multiple phases of care may be challenging. This is especially the case for modern warfare where blast injuries and their sequelae are common. In order to improve adherence to DCR principles, researchers from the University of Pennsylvania and the Uniformed Services University of the Health Sciences created a clinical decision support system called "Hemorrhage Helper" to improve adherence to DCR principles using an iterative development and human factors testing approach (Schmulevich et al., 2021).

Study participants consisted of trauma surgeons and fellows, anesthesia providers, and trauma bay and intensive care unit nurses. Participants provided qualitative and quantitative feedback on the initial prototype and all subsequent iterations of the clinical decision support system. Considerations were made for the initial needs assessment and prototype design (Phase 0), testing in a multi-dimensional simulation (Phase 1), and testing during initial clinical use (Phase 2). All phases of testing included hands-on use of the decision support system in the trauma bay, operating room, and intensive care unit.

In a review of Hemorrhage Helper, 87.5 percent of participants noted they would use the clinical decision support system in a clinical setting. Additional iterative testing involved trauma team members participating in simulated resuscitations with the clinical decision support system, where about 78 percent of 228 tasks were passed and 11.8 percent or 27 tasks were passed with difficulty. Once improvements were made to the design of Hemorrhage Helper, Phase 2 evaluation included 21 trauma team members during multiple real-world trauma resuscitations. Feedback on the device via a Likert scale (range

0 - 4) confirmed overall ease of use (median score = 4; interquartile range = 44) and indicated the system integrated well into their workflow (median score = 3; interquartile range = 2 - 4). As a result, researchers completed final refinements in preparation for a pilot study using Hemorrhage Helper. The development of clinical decision support tools can greatly assist in the treatment of trauma, particularly hemorrhage, which often results from complex blast injuries. This research was published in the *Journal of Trauma and Acute Care Surgery* (Schmulevich et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Assessment of Damage-Control Resuscitation Hemorrhage Transfusion Ratios

Warfare post-9/11 and post-Afghanistan often involved blast trauma, which often results in hemorrhage, a major cause of casualties. Damage-control resuscitation (DCR) principles improve survival in severely bleeding patients. However, deviating from balanced transfusion ratios during a resuscitation may limit this benefit. Researchers at the University of Pennsylvania hypothesized that maintaining a balanced resuscitation during DCR is independently associated with improved survival and incorporated this vital question as a secondary analysis of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study. Hemorrhaging patients receiving more than three units of packed red blood cells (PRBCs) during any one-hour period over the first six hours and surviving beyond 30 minutes were included. Many parameters were considered to assess 24-hour and 30-day survival with respect to use of blood product ratio being "on-target" or "off-target" (above threshold), and multivariable logistic regression identified all independently associated factors. Of 1,245 patients enrolled in the PROMMTT study, 524 met the criteria to be included. Optimal targets were plasma/PRBC and platelet/PRBC of 0.75 (3:4) and 40 percent or more time spent over this threshold. After adjusting for differences, on-target plasma/PRBC patients significantly improved 24-hour (odds ratio, 2.25; 95 percent confidence interval, 1.20–4.23) and 30-day (odds ratio, 1.97; 95 percent confidence interval, 1.14–3.41) survival, while on-target platelet/PRBC patients did not. Maintaining a high ratio of plasma/PRBC during DCR is independently associated with improved survival rates. These results reinforce that performance improvement efforts and prospective studies should capture time spent in a high-ratio range. Usage of clinical decision support systems such as "Hemorrhage Helper" can greatly improve adherence to DCR principles, better track these parameters, and greatly improve survival from blast traumas. This research was published in *J Trauma Acute Care Surg* (Hynes et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Improving Cerebral Perfusion with Drag-Reducing Polymers

Hemorrhagic shock in polytrauma may lead to impaired cerebral blood flow and perfusion pressure, resulting in brain injury. Standard therapy for hemorrhage includes fluids to expand blood volume, followed by blood transfusion. However, the use of certain volume expanders may injure the brain by causing swelling and tissue death. Researchers at the University of New Mexico Health Sciences Center and the Lovelace Biomedical Research Institute demonstrated that adding drag-reducing polymers to hydroxyethyl starch (Hetastarch) resuscitation fluid, compared to the use of Hetastarch alone,

provided protection of the brain because a smaller volume of fluid was required for resuscitation. The use of improved resuscitation fluids that treat hemorrhage, while protecting other organs from fluid overload, may result in fewer post-trauma injuries for Service members. This research was published in *Acta Neurochir Suppl.* (Bragin et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Comparing Fresh Frozen Plasma to Colloid Fluid in Lung Injury Hypotensive Resuscitation

Among those severely injured in civilian and military settings, a leading cause of early death is hemorrhagic shock. In a prolonged care environment with limited resources, the use of whole blood and blood components in prescribed ratios are ideal but may not be practical. This study, by researchers at the University of Maryland, Baltimore investigates the role of fresh frozen plasma (FFP) versus colloid resuscitative fluid (Hextend) in a prolonged hypotensive resuscitation model. The animal model demonstrates that resuscitation with FFP reduces lung injury, inflammation, and permeability compared to Hextend. This study provides further support to remove Hextend from prolonged field care guidelines, as there is a potential additional detrimental effect on the lungs, a critical consideration for blast injury which can be associated with lung damage. This research was published in *J Trauma Acute Care Surg* (Chipman et al., 2020).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Hypothermia to Reduce Complications from Treatment of Non-Compressible Hemorrhage

Placement and inflation of a balloon in the aorta (resuscitative endovascular balloon occlusion of the aorta, (REBOA)), may treat non-compressible torso hemorrhage. Although aortic occlusion may be lifesaving in the short-term, further injury may be caused by prolonged use, which can reduce or eliminate blood flow to other organs or extremities — contributing to blood complications and resulting in ischemia-reperfusion injury when blood flow returns to the blood- and oxygen-starved organs. This injury can, in turn, lead to a systemic inflammatory response, resulting in significant post-treatment injury. In this project, conducted in an animal model, researchers at the University of Maryland, Baltimore used a novel transrectal intra-colon device with REBOA to cool the abdomen to 12°C, providing focal rather than systemic hypothermia. This method was associated with reduced organ injury, inflammation and infection biomarkers, and mortality. The use of this technology may help reduce complications related to the control of hemorrhage resulting from blast injury. This research was published in *Sci Rep.* (Arya, Hu, Subedi, Li, & Hu, 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

A Non-Invasive Technique to Measure Cerebrovascular Autoregulation Following Injury

Cerebrovascular autoregulation (CA) is a protective mechanism that enables the cerebral vasculature to automodulate tone in response to changes in cerebral perfusion pressure to ensure constant levels of cerebral blood flow (CBF) and oxygen delivery. CA can be impaired after neurological injury, such as from blast trauma, and contributes to secondary brain injury. In a recent study, researchers at the University of Michigan reported

Photo credit: Lance Cpl. Mackenzie Binion/U.S. Marine Corps

novel impedance indices using trans-ocular brain impedance (TOBI) during controlled systemic hemorrhage and hypotension to assess CA in comparison with pressure reactivity index (PRx) (Tiba et al, 2021). In the study, Yorkshire swine were used to record intracranial pressure (ICP), mean arterial pressure (MAP), and CBF. TOBI was recorded using electrocardiographic electrodes placed on the closed eyelids. Impedance changes (dz) were recorded in response to introducing an alternating current (0.4 mA) through the electrodes.

Animals were subjected to a controlled hemorrhage to remove 30–40 percent of each animal's total blood volume over 25–35 minutes. Hemorrhage was titrated to reach an MAP of approximately 35 mm Hg and end-tidal carbon dioxide above 28 mm Hg. PRx was calculated as a moving Pearson correlation between MAP and ICP.

The study showed that dz was highly correlated with MAP, ICP, cerebral perfusion pressure, and CBF. During severe bleeding, cerebral perfusion pressure and CBF had a mean percent decrease (standard deviation) from baseline of −54.2 percent (12.5 percent) and −28.3 percent (14.7 percent), respectively, whereas dz increased by 277 percent (268 percent).TOBI indices appear to track changes in PRx and hemodynamics that affect CA during hemorrhage-induced hypotension. TOBI may offer a suitable, less invasive surrogate to PRx for monitoring and assessing CA which could be particularly useful for blast-related closed-head injuries.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/ Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

HmC–hmA Foams as Hemostatic Agents to Treat Torso Trauma

Non-compressible abdominal bleeding is a leading cause of preventable death in both military and civilian settings and accounts for 85 percent of all hemorrhage fatalities. The use of foam with an active hemostatic agent is a compelling method for treating these complex injuries, but it generally cannot resist blood flow at the wound site. Researchers have done tremendous work to develop a new class of foam with enhanced rheological properties, resulting from two amphiphilic polymers reacting to form an improved blood-barrier foam which can also subsequently be dissolved. Their work in animal wound models demonstrates that hmC–hmA foams with hemostatic agents are promising therapies for complex torso injuries which can often result from blast trauma. This research was published in ACS Appl Mater Interfaces (Choudhary, Rudy, Dowling, & Raghavan, 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Non-Invasive Methods for Monitoring Cerebral Blood Flow from Decompensated Hemorrhagic Shock

Decompensated hemorrhagic shock (DHS), often resulting from blast injuries, is the leading cause of preventable death in combat casualties. Currently, only invasive techniques such as partial pressure of oxygen (PtO2) and mean arterial pressure (MAP) are viable for resuscitation. Using an established non-human primate model of DHS, researchers tested the efficacy of noninvasive regional tissue oxygenation (rSO2) and Transcranial Doppler (TCD) methods in guiding hypotensive resuscitation. Although the study findings did not correlate strongly enough to warrant implementation of these non-invasive techniques in a prolonged field care setting, this work showed they effectively augment and direct resuscitation and could serve as a backup method should there be no capability to use the invasive methods. Combat casualties often involve complex blast injuries resulting in DHS, and continued studies into these non-invasive treatment methods could improve "Golden Hour" resuscitative guidelines. This research was published in *Shock* (Morgan et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Percutaneous Trigeminal Nerve Stimulation Induces Cerebral Vasodilation in a Dose-Dependent Manner

Constriction of cerebral blood vessels can lead to cerebral vasopasm and disrupt the mechanisms that ensure adequate blood supply to the brain. Stimulation of the trigeminal nerve can directly modulate cerebral blood flow via these networks. The present study demonstrates that percutaneous electrical stimulation of the infraorbital branch of the trigeminal nerve increases brain calcitonin gene-related peptide, thereby producing controllable cerebral vasodilation. This electrical stimulation of the infraorbital nerve significantly improved cerebral vasopasm in an animal model of subarachnoid hemorrhage and could lead to a promising new treatment approach in humans.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Medical Simulation and Information Sciences Research Program/Joint Program Committee-1.

Mathematical Models Evaluating Closed-Loop Resuscitation Control Algorithms

Results obtained from comparing characteristics of physiological closed-loop control (PCLC) response under the use of the mathematical model versus animal subjects gauge the effectiveness of the validated mathematical model in PCLC assessment. The results will provide a mathematical model and simulation methods for in silico evaluation of automated fluid resuscitation and vasopressor infusion systems that may serve as a regulatory science tool supported by robust validation evidence. Results will also provide a framework that can be followed by other mathematical model developers to generate evidence and establish the credibility of computational simulations for other types of PCLC devices (e.g., ventilators). Future autonomous closed-loop resuscitation systems well validated with extensive in silico safety and efficacy testing based on mathematical models will allow medics, forward surgical teams, and combat support hospitals to apply resuscitation therapies near equivalent to those of the trauma center standards.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Medical Simulation and Information Sciences Research Program/Joint Program Committee-1.

Comparison of High Versus Low Volume Fluid Resuscitation Strategies in a Swine Model of Burn/TBI

Blast exposure may result in combined burn injury and TBI. Increased complications result from this polytrauma compared to burn or TBI alone. Each injury requires opposing methods of fluid management, making it difficult to know how to best treat combined burn/TBI. Burn treatment requires high-volume fluid resuscitation, whereas TBI treatment requires limited fluid resuscitation to avoid cerebral edema.

Researchers at the University of California, Davis, compared aggressive, high fluid and restrictive, low fluid resuscitation strategies in a swine model of combined burn/TBI. Anesthetized swine (n = 28) received either the aggressive or restrictive fluid resuscitation strategy after combined burn/TBI and were monitored for eight hours. Researchers measured the increase in intracranial pressure after combined burn/TBI, and they found no difference between the resuscitation strategies. Overall, both strategies seemed to provide adequate resuscitation in the first eight hours, with no significant differences in brain injury, heart rate, blood pressure, or central venous pressure. This model will continue to be used to further analyze resuscitation strategies at longer timepoints, with a focus on the effects of renal and neurological functions. This will allow for a better understanding of how to treat patients with combined burn injury/TBI.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Comparison of Fish Skin to Cadaver Skin as Temporary Coverage for Full-Thickness Burns

A research team conducted a pilot clinical evaluation of human subjects with full-thickness burns by treating the subjects with both fish skin and human cadaver skin as a temporary coverage of burn wounds. The research generated preclinical animal data, which was used to support an FDA Investigative Device Exemption (IDE). Previous completed preclinical animal model in pigs conducted at the U.S. Army Institute of Surgical Research successfully duplicated results obtained in another animal study that was conducted in Iceland.

Photo credit: Capt. Nicholas Royer/ U.S. Marine Corps

The results supported the safety and efficacy of the use of the Kerecis processed fish skin as an early coverage for burn wounds. The animal data led to the FDA IDE approval and allowed for the initiation of human subject research following approvals issued by the institutional review board and the Human Research Protection Office at the U.S. Army Medical Research and Development Command. Results accomplished during FY21 included completion of the pilot, human clinical evaluation in five burn subjects enrolled at the MedStar Health Research Institute in Washington, D.C. that included a 12-month follow-up period. Total body surface area of burns ranged from 8-37 percent, and the body mass index of subjects ranged from 20-27. Per the final technical report, the Kerecis processed fish skin treated sites showed comparable epidermal thickness to allograft treated sites (based on histological analysis performed on biopsies from two subjects). In addition, statistical analysis on the five subjects "revealed no significant differences between the groups for graft take, healing, pain, and scarring" and showed that all burn wounds healed with comparable outcomes and appearances regardless of treatment (fish skin or allograft). The authors concluded that the results "indicate that fish skin grafts are an efficient and safe alternative to cadaver skin as early cover for full thickness burns."

This effort was supported by the Military Burn Research Program with program interest from the Combat Casualty Care Research Program/Joint Program Committee-6.

Novel Bone Void Fillers for Point-of-Care Treatment of Open Fractures

Researchers at Vanderbilt University reported notable findings regarding the use of resorbable bone void fillers (BVF) at the point of care to enhance healing of open fractures (McGough et al., 2020). This is particularly relevant to blast injury as intra-articular fractures secondary to explosions, fragment projectiles, and gunshot wounds are the most common causes of injury that result in post-traumatic osteoarthritis (PTOA). The prevalence of PTOA in combat-wounded Service members is 28 percent, compared to 12 percent in the civilian trauma population. Poor articular reduction, joint instability, and malalignment of tibial plateau fractures can contribute to poor outcomes in the knee, including PTOA and early total joint arthroplasty. BVFs with bone-like strength are anticipated to improve articular reduction and joint stability, thereby improving outcomes. The results published suggest that nanocrystalline hydroxyapatite (nHA)–poly(thioketal urethane) (PTKUR) cement, when injected in femoral defects in a preclinical model to evaluate ossification, supports combined intramembranous and endochondral ossification, resulting in enhanced osseointegration of the cement that could potentially improve patient outcomes.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Combinational REBOA & Pharmacological Treatment of Hemorrhagic Shock Traumatic Brain Injury and Complex Vascular Injuries

Hemorrhage on the battlefield, often resulting from blast trauma, is the leading cause of mortality in Service members. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) can control excessive bleeding; however, distal ischemia, subsequent reperfusion injury, and the need for frequent balloon titration remain problematic. An improved device design that allows for partial REBOA (pREBOA) may provide hemorrhage control while also perfusing distally without the need for significant titration. As such, a recent study (Kemp et al., 2021) published results regarding the use of pREBOA in a preclinical model of hemorrhage. The study found that an improved design for pREBOA can help these issues by decreasing the degree of distal ischemia and reperfusion injury compared with complete aortic occlusion while providing a similar increase in proximal mean arterial pressure. The improved design allows pREBOA zone-1 deployment for more extended periods without the need for significant balloon titration.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Evaluating Novel Metabolic Stabilizing Agents Incorporated into Limited Volume Resuscitation Fluids Post-Traumatic Injury

Investigators at the U.S. Army Institute of Surgical Research are investigating novel therapeutic options for reducing inflammation and hypermetabolism due to traumatic injury. The approach involves examining the capacity of metabolic stabilizing agents to reduce or delay multiple organ failure when used as adjuncts to resuscitation in a 40 percent total body surface area swine model. Identification and down-selection of promising new therapeutic candidates to test efficacy in the large animal model is underway. This effort holds potential to deliver the capability to administer lower fluid resuscitation volumes while optimizing recovery of burn casualties and other trauma, avoiding the danger of delivering too much fluid, and reducing the logistical burden of resuscitative interventions at all echelons of care. Outcomes of this work are likely transferable into beneficial impacts for resuscitative care of burn and other traumatically wounded patients in the civilian public sector and for both military and civilian mass casualty events.

Funding support provided by the Combat Casualty Care Research Program.

Preclinical and Clinical Evaluations of Field-Deployable Non-Surgical Debridement Methods for Severe Burn Wounds

The U.S. Army Institute of Surgical Research is continuing to study, in a militarily-relevant porcine model, the efficacy of a novel, advanced non-surgical technology to remove burned, dead tissue from the wound bed (non-surgical debridement), which can otherwise reduce burn wound healing potential by releasing toxins and serving as a matrix for infection.

Necrotic, burned tissue resulting from thermal injury is typically removed from the body via surgical debridement (i.e., surgical excision of dead, burned tissue to reduce danger of infection and provide a healthy wound bed to enable best possible healing), followed by skin grafting to close the wound over a period of weeks or months. However, this standard of care procedure can only be performed in a surgical suite and is commonly associated with blood loss and the unfortunate removal of viable healthy tissue during surgeries. For some patients and contexts such as extended care on the battlefield, it would be preferable to remove devitalized tissue with a non-surgical debridement agent.

The current effort will determine whether the novel technology is compatible for use on already infected wounds and with simultaneous administration of topical antimicrobial treatments. Testing of the novel debridement solution in a pig model of an infected burn wound, as well as testing of the technology applied in conjunction with topical antimicrobials in lab assays, is underway, showing success to date. Evaluation of the combination treatment in the pig burn wound model is pending. Dependent on available funding, clinical assessments of the novel therapy are planned for the near future.

Funding support provided by the Combat Casualty Care Research Program.

Evaluation of Off-the-Shelf Therapies to Improve Severe Burn Injuries and Accelerate Return to Duty

Burn researchers at the U.S. Army Institute of Surgical Research (USAISR) are identifying promising off-the-shelf (OTS) therapies that can promote healing of severe burn wounds equivalent to standard of care. Large animal burn wound models are being used to test administration of candidate solutions in a simulated prolonged care, burn injury model, in comparison to treatment using the anti-infective, moisture-retaining topical cream Silvadene, approved by the U.S. Food and Drug Administration and commonly used to treat burns in the field today.

The OTS candidates are also being evaluated for the capability to potentiate healing outcomes at least as well as the standard of care for deep partial-thickness wounds, when candidates are administered following use of an experimental, non-surgical, topical, enzymatic debridement agent to remove dead, burned tissue from the wound (novel debridement technology as described in the USAISR effort above).

The goal of these parallel studies of OTS agents is to optimize a set of acute burn injury management techniques to reduce the need for auto-grafting, while hopefully easing the path to regulatory approval for our expanded indication and possible combination debridement and healing-encouraging therapy.

Identified candidates have been tested in debrided, deep partial-thickness burn wounds for down-selection. Validation of agent efficacy in a militarily relevant large animal model is underway. If successful, future studies will include human safety and efficacy testing for the individual OTS products, as well as OTS product(s) in combination therapy with the novel, non-surgical debridement tool. Test candidates alone or in combination may yield accelerated and/or otherwise improved healing outcomes for severely burned military and civilian patients.

Funding support provided by the Combat Casualty Care Research Program.

Early Post-Burn Treatment to Reduce Injury Progression and Bioburden

A study in progress by burn researchers at the U.S. Army Institute of Surgical Research is identifying and incorporating anti-inflammatory and antimicrobial agents for use in a novel patch dressing, which when applied soon after burn injury is capable of reducing the problem of burn wound progression (worsening wound depth and size that occurs in the early hours after burns are incurred). Early efforts narrowed down promising anti-inflammatory and antimicrobial agents, which now have been fabricated into test patch materials for further study. Next steps are to assess efficacy of the novel materials to reduce microbial burden and burn wound progression in a large animal burn injury model.

Success with this work will underpin the potential of this approach to represent a significant step toward delivery of a major breakthrough tool for acute management of severe burn injuries, for which no proven safe and effective means of

Photo credit: Spc. Rachel Christensen/ U.S. Army

mitigating burn progression exist. These patch materials, once assessed in human trials, may provide an easy-to-use dressing capable of protecting the wound bed early post-injury and delivering a first-in-class human therapy to actively intervene in the dysfunctional physiology driven by burn wounding in order to preserve and promote healing of potentially salvageable unburned skin.

Funding support provided by the Combat Casualty Care Research Program.

Far Forward Treatments to Prevent Burn Progression

Researchers at the U.S. Army Institute of Surgical Research are evaluating potential treatments targeting poor blood perfusion and dysregulated inflammation as potential topical treatments for deployment in far forward settings to reduce burn wound progression (worsening wound depth and size that occurs in the early hours after burns are incurred). Delivery of anti-ischemic and anti-inflammatory agents, alone or in combination, to the burn wound bed early after burn injury may mitigate the tendency for burn wounds to deteriorate due to physiological processes impacting burn wound status even in the absence of microbial contamination and infection. Assessment of therapeutics to mitigate dysregulated inflammation and poor blood perfusion to the burn wound post-injury has been completed in a porcine burn wound model. Next steps involve testing of a combination of promising agents for ability to prevent burn wound progression in the large animal to transition the potential therapy to human studies. The capability to mitigate burn wound progression will reduce the extent of required follow-on care and need for grafting, improve functional recovery of burn casualties, and hasten return to duty.

Funding support provided by the Combat Casualty Care Research Program.

Alginate-Plasma-Based Dressing to Treat Combat Associated Wounds

Investigators at the U.S. Army Institute of Surgical Research have completed early studies toward development of an advanced, therapeutic burn wound dressing that maintains wound bed hydration and delivers a mixture of biological factors derived from cellular vesicles with capability to stabilize the wound, support an appropriate inflammatory response following burn injury, and drive a healing response. A wound dressing capable of releasing the target biologics was developed and characterized in immune cell assays in the laboratory. Next steps will assess the dressing in a militarily relevant porcine burn wound model.

Funding support provided by the Combat Casualty Care Research Program.

Cerium Nitrate Treatment of Burns: Effect on Injury Progression and Epithelialization in a Pig Model

The U.S. Army Institute of Surgical Research is conducting research to develop an ultralight, bio-resorbable thin-film or textile-based dressing that will cling to irregular-surface wounds and deliver the therapeutic agent cerium, alone or in combination with silver, to severe burns when applied at the point of need, in order to stabilize the wound, reduce injury progression and microbial contamination, and accelerate healing beginning in the pre-hospital environment. The cerium thin-film dressing did not reduce burn wound progression when assessed in a porcine model of deep-partial thickness burn injury. Assessment of the capability of cerium thin-films to reduce microbial bioburden is ongoing. Testing the ability of the dressing to accelerate cellular regrowth to hasten wound closure will be conducted, with the goal of stabilizing the burn wound to enable safe delay of casualty evacuation while already promoting burn injury healing outcomes in the far forward environment prior to the availability of surgical care.

Funding support provided by the Combat Casualty Care Research Program.

Determination of Optimal Intraosseous Infusion Techniques

Intraosseous (IO) infusion is an important vascular access technique used by military first responders to infuse fluids and blood when intravenous (IV) access is difficult or unobtainable. The purpose of a recent project is to determine the optimal IO infusion technique, identify which IO devices are preferred by providers, and demonstrate how IO placement affects flow and pressures generated during infusion. Data will be gathered from multiple IO devices and different infusion strategies in an ex vivo model. Optimal strategies and devices will then be tested in an in vivo animal model of hemorrhagic shock and will assess the relationship of IO infusion pressure to secondary injuries such as fat emboli, bony injury, and red blood cell destruction. Results of this study will be used to develop a computational IO infusion model for further study to improve techniques and devices. Initial findings from this project have already informed clinical practice (Tactical Combat Casualty Care Tactical Field Care: IV/IO Access Module) and will improve care for critically injured Service members, including those injured by blast, in austere settings where vascular access is challenging and resuscitation is key to survival.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

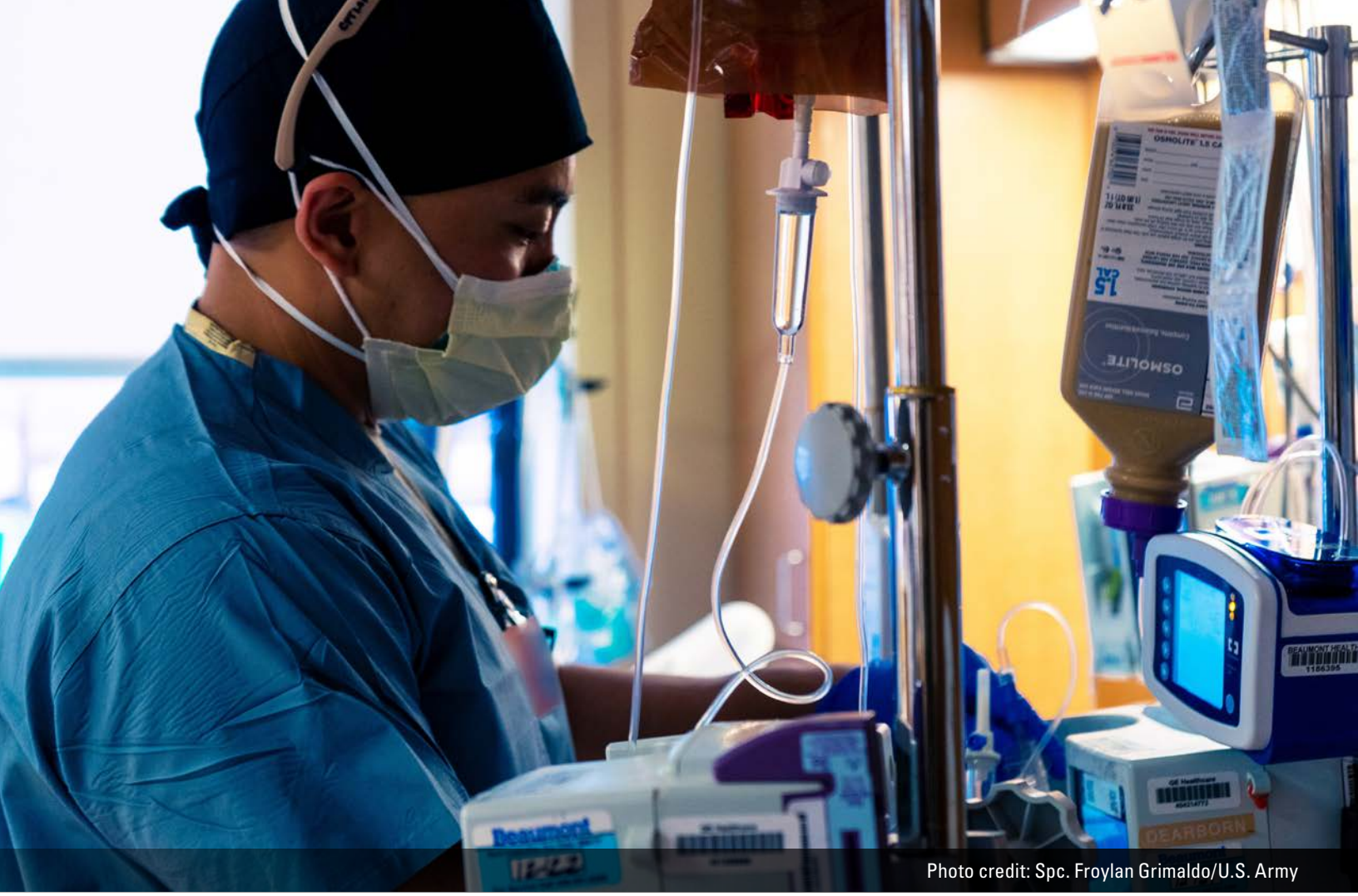


Photo credit: Spc. Froylan Grimaldo/U.S. Army

The Gastroesophageal Resuscitative Occlusion of the Aorta as an Alternative Method for Rapid Control of Non-Compressible Torso Hemorrhage

Researchers at the University of Michigan, Michigan Center for Integrative Research in Critical Care are studying the Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for treatment of non-compressible torso hemorrhage (NCTH) is effective but requires vascular access, imaging-guided placement, and surgical skill, all of which are limited in austere environments. As an alternative method for rapid control of NCTH in pre-hospital and field care settings, a research team (Tiba et al., 2020) has developed a prototype device and approach. The Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) device is inserted via the esophagus into the stomach, which lies next to the aorta. It does not require surgical or imaging techniques to apply and deploys in minutes. In animal testing, the GROA demonstrated similar physiological effects and tolerance up to 90 minutes of occlusion, compared to REBOA.

This effort was managed by the Congressionally Directed Medical Research Programs with support and programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Reset

Reset describes a concept that extends beyond rehabilitation to include all activities necessary to return injured Service members to duty or to productive civilian life. Reset includes research to advance strategies for reducing recovery time, improving rehabilitation programs, maximizing opportunities for return to duty and reintegration into the civilian workforce, and improving the quality of life for Service members who have experienced blast-related injuries. Reset accomplishments from FY21 are organized into four categories: reconstruction and prosthetics; secondary injury and comorbidities; prolonged care; and consortium studies.

Reconstruction and Prosthetics

Biomechanical Characterization of the Foot-Ground Interaction Among Service Members with Unilateral Transtibial Limb Loss

The purpose of this study, conducted by researchers from the Research & Surveillance Division of DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE), was to biomechanically characterize foot-ground interactions during drop-landings. Study participants included seven male Service members with, and seven without, unilateral transtibial limb loss. The study was undertaken because of the lack of data to guide methodology development for evaluating the impact resilience of prosthetic ankle-foot systems, particularly looking at ecologically valid scenarios that involved human-device interaction.

Participants completed six drop-landing scenarios, which consisted of three heights and two loads (with and without a 22.2 kg weighted vest) in different combinations. Comparisons were made across groups, evaluating vertical ground reaction forces (GRF) loading rate and impulse, peak GRF, and ankle-foot, knee, and hip joint negative (absorption) powers and work, by height and load conditions. Results showed that loading occurred primarily in the vertical direction and increased with added load and/or increasing drop height. On the prosthetic side, vertical GRFs were overall approximately 15 percent smaller (versus controls) with similar loading rates across limbs/groups. In the most challenging scenario, ankle-foot absorption energies on the prosthetic side were 64.6 (7.2) J; corresponding values were 187.4 (8.9) J for the contralateral limb and 161.2 (6.7) J among uninjured controls. This research was published in the *Journal of Biomechanics* (Elrod et al., 2021).

These efforts were conducted at Walter Reed National Military Medical Center by investigators from the Research & Surveillance Division of the DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE) and supported by funding to the BADER Consortium from the Peer Reviewed Orthopaedic Research Program (W81XWH-11-2-0222).

Assessments of Trunk Postural Control within a Fall-Prevention Training Program for Service Members

Trunk postural control (TPC) is critical in maintaining balance following perturbations (i.e., avoiding falls). TPC is impaired among persons with lower extremity trauma, which contributes to increased fall risk. A previous fall-prevention program showed improved TPC in individuals with unilateral transtibial amputation following trip-inducing perturbations; however, it is unclear if these improvements are linked to specific tasks. Included in this analysis were twenty-five persons (21 male and four female) with lower extremity trauma, who all participated in a larger fall-prevention program.

In this study, accelerometer-based sway parameters measured TPC during unstable sitting, and trunk flexion and flexion velocity measured TPC following perturbation. Training-induced differences in TPC after perturbation were assessed by a

generalized linear mixed-effects model, while differences in sway parameters following training were assessed by a generalized linear model. Following perturbation, researchers used Spearman's rho to relate training-induced changes to TPC (i.e., the difference in TPC measures at pre- and post-training assessments) with pre- versus post-training changes to sway parameters during unstable sitting, (i.e., the difference in sway parameters at pre- and post-training assessments) as well as pre-training sway parameters with the pre- versus post-training differences in TPC following perturbation.

Analysis revealed that sway parameters did not differ pre- and post-training; however, trunk flexion angles decreased following training, indicating improved TPC. In addition, pre- versus post-training differences in TPC following perturbation were neither strongly nor significantly correlated with sway parameters. Finally, pre-training sway parameters did not correlate with pre- versus post-training differences in trunk flexion or flexion velocity. This research was published in Gait Posture (Acasio et al., 2021).

These efforts were conducted at Walter Reed National Military Medical Center by investigators from the Research & Surveillance Division of the DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE) and received support from the Orthotics and Prosthetics Research Program (Award W81XWH-15-2-0071).

A Robotic Prosthetic Foot Emulator Enables Patients with Amputation to "Test Drive" Different Prosthetic Feet

Prosthetic foot selection is critical to enabling people with amputation to return to their normal activities (including return to duty). The patient is often not able to try on multiple feet within one session, and it is not clear if what a patient prefers in the clinic represents what they prefer after a take home trial. The Prosthetic Foot Emulator (PFE) can mimic the characteristics of different types of prosthetic feet, as well as individual feet of different stiffness categories. Allowing patients to "test drive" various prosthetic foot designs during a single testing session, without requiring a change in prosthetic hardware, offers the potential to augment the prescription of prosthetic feet, thereby restoring performance of Service members with lower limb amputation. In this study, a research team led by scientists at the Seattle VA, in collaboration with Extremity Trauma and Amputation Center of Excellence and the Minneapolis VA, worked to determine whether a brief in-lab trial of prosthetic feet could predict longer-term foot preference. In short, the ability for a patient to "test drive" prosthetic feet would enable them to optimize their prescription faster, thus enabling a more rapid return to their community.

A total of 68 active-duty Service members and Veterans with transtibial amputation trialed three commercial prosthetic feet and three corresponding emulated feet using a robotic prosthetic foot emulator, which can quickly switch candidate feet, primarily via a software interface. Participants walked in different conditions (e.g., level and inclined treadmill, stairmill) in each emulated and commercial foot. Participants then wore each commercial foot for two-week community trials. Experiential foot preference was recorded during in-lab and post-community trials for all feet, on a 0–10 scale, across areas including satisfaction, willingness to use, and perceived energy to use.

These efforts were conducted within the Center for the Intrepid at Brooke Army Medical Center by investigators from the Research & Surveillance Division of the DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE), in collaboration with the Seattle VA and the Minneapolis VA. This work received support from the Orthotics and Prosthetics Research Program (Award W81XWH-16-1-0569).

Determining Long-Term Use and Return to Duty Rates Following Intrepid Dynamic Exoskeletal Orthosis Prescription

The Intrepid Dynamic Exoskeletal Orthosis (IDEO) is an energy storage and return orthotic device developed at the Center for the Intrepid. These custom orthoses have allowed limb salvage patients with severe lower extremity injuries to return to active duty and high-level activities. Previous studies revealed that 20 percent of these patients will elect amputation within 12 months of injury; however, middle and long-term outcomes for IDEO users are not known. This pilot study was designed to evaluate whether IDEO users with a variety of severe lower extremity injuries still use their IDEO more than two years following injury, and to identify what impact this use has had on their ability to return to duty, work, and recreational activities.

A total of 55 individuals (which included Veterans, active-duty Service members, and dependents) who had been prescribed an IDEO more than two years prior to the initiation of the study were contacted by phone. All patients had received their IDEO and had undergone rehabilitation at the Center for the Intrepid. Participants were asked a series of questions about their IDEO use (or lack thereof); reason(s) for ongoing use or for abandonment; relevant surgical history, including amputation; and military occupation and work status before and after device prescription. Additional information such as demographic data, mechanism of injury, number of prescribed IDEOs, and rehabilitation history was collected from the medical record. Of the 55 participants recruited for this pilot study, two-thirds (37) were using their IDEO at least two years following prescription.

The majority of subjects suffered lower extremity fractures and/or sprains (50.9 percent) or had sequelae of explosive injuries (23.6 percent). One-third of subjects (20) were able to return to active duty or to their previous occupation. Five patients (9.1 percent, three of whom were treated for blast injuries) elected to undergo amputation. These data indicate that the majority of limb salvage patients who are prescribed an IDEO will continue using the IDEO without electing amputation.

Photo credit: U.S. Army

These efforts were conducted within the Center for the Intrepid at Brooke Army Medical Center by investigators from the Research & Surveillance Division of the DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE) and received support from the EACE.

Characterization of Combat-Related Lower Extremity Limb Salvage in the Military Health System

Using a recently validated data-driven approach for identifying Service members with lower extremity limb salvage (LS), researchers first characterized the demographics, concomitant injuries, acute complications, secondary health effects, and clinical resource utilization of Service members with combat-related LS within the Military Health System (2004–2016). Researchers then compared subsets of this population based on successful limb retention (i.e., no amputation [NA], secondary amputation [SA]) with cohorts that received primary amputations (PA) or otherwise experienced limb trauma (LT) that did not meet the definition of LS.

No differences were observed between any of the cohorts for the following demographic variables: sex, branch of the military, and paygrade. The

mechanism of injury was found to be different between the cohorts, owing to higher rates of blast-induced injuries and lower rates of gunshot wounds among the LS population. Accordingly, the LS cohort exhibited a greater mean Injury Severity Score (ISS) compared to LT. The LS–SA cohort experienced a disproportionate rate of blast injury, exhibited a higher mean ISS, and received a higher maximum lower extremity Abbreviated Injury Scale relative to the LS–NA cohort.

A number of injuries were more prominent within the LS cohort, including fracture of the skull, fracture of upper limb, intracranial injury, and injury to blood vessels. Concomitant injuries that were less likely to occur in the LS cohort relative to the LT cohort included fracture of the spine and trunk, as well as internal injury of the chest, abdomen, and pelvis. The PA and LS–SA groups were found to experience higher rates of acute complications compared to the LS–NA and the LT groups. Out of the 19 complications examined, the LS–SA group had the highest rates in 12 complications and the PA group the highest in 7. The majority of the complications exhibited the highest incidence rates in the first three months.

Of the 30 secondary health conditions examined, 26 presented disparately amongst the groups. The most prevalent diagnosis in the PA and LS-SA groups was other soft tissue disorders, whereas joint pain was the most prevalent for LS–NA and LT. After adjusting for covariates, PA, LS–SA, and LS–NA were more likely to have pain, other derangement of knee, and pain in limb than the LT cohort. The LS–SA cohort exhibited the highest mean number of ICU bed days. Within one year of injury, the total study sample averaged over 200 visits to outpatient clinics. The PA group had a higher number of outpatient clinic visits than all other groups. Engagement was highest in the physical therapy clinic, followed by orthopedics, social work, occupational therapy, and primary care.

This effort was conducted by investigators located at the Uniformed Services University of the Health Sciences from the Research & Surveillance Division of the DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE) in collaboration with the Naval Health Research Center and was supported by funds from the EACE.

Patent for 3D Bioprinting of Devices and Scaffolds for Tissue Repair

Damage to the upper and/or lower extremities is becoming an increasingly common injury among those sustained by Service members. Treatment of these wounds requires complex reconstructive procedures and the replacement of damaged or lost bone. Conventional methods for the regeneration of long bone injuries involves transplantation of autografts. However, this method is not always feasible for those severe injuries where a donor site for grafting is not available.

A team of scientists at New York University School of Medicine received an FY15 award from the Reconstructive Transplantation Research (RTR) program to investigate an alternative strategy for the repair of long bone injuries. The investigators have patented their method of 3D printing tissue repair devices, or scaffolds, made of a resorbable calcium- and phosphorus-based ceramic material. The team has previously demonstrated the ability of the developed scaffold to directionally regenerate and remodel bone, as well as its biocompatibility and resorption. These scaffolds may be used to promote bone growth following traumatic injuries.

This effort was supported by the Reconstructive Transplant Research Program with program interest from the Combat Casualty Care Research Program/Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

World's First Successful Combination Face and Double Hand Transplantation

Extremity trauma and amputations and severe craniofacial injuries represent a severe disease burden and cause a great degree of disability for both Service members and civilians. Vascularized composite allotransplantation (VCA) is a reconstructive option for these types of severe traumatic injuries. VCA involves the transplantation of multiple tissues as a functional unit (e.g., a hand or face) to replace like with like with the goal of returning injured Service members to duty and restoring their quality of life.

A team of scientists and doctors at New York University completed the world's first successful combination face and double hand transplantation, funded in part with an FY14 clinical trial award through the Reconstructive Transplantation Research Program (RTRP). The patient was in a car accident when he suffered third-degree burns covering 80 percent of his body and face, requiring his fingertips to be amputated. Two years after his injury, the patient underwent a 23-hour operation to transplant a face and both arms from a deceased donor. 3D computer surgical planning and 3D-printed patient-specific cutting guides were used for proper alignment and anchoring of transplanted tissues as well as for optimizing functional and aesthetic outcomes of the procedure. This approach is expected to minimize immunosuppression while improving function and thereby expand the clinical use of VCA for reconstruction of a wide range of traumatic and post-ablative injuries in both civilians and combat Veterans. Apart from standardization of VCA surgical process and protocols, the development of personalized surgical devices and design process has the potential for the VCA procedure to be customized for each patient based on their unique anatomy. The team is working on using this technology to generate a 3D measurement system to evaluate and understand long term outcomes of the allografts. Also, immune profiling-based non-invasive method of allograft surveillance to predict acute rejection is being developed.

The patient is doing well and remains highly engaged and motivated in rehabilitation and recovery.

This effort was supported by the Reconstructive Transplant Research Program with program interest from the Combat Casualty Care Research Program/Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Mapping the Inflammatory Response to Vascularized Composite Allotransplantation

For catastrophically injured Service members, hand and/or face transplantation may be a viable option for restoring quality of life and function. These types of transplants are called vascularized composite allotransplantation (VCA) and involve the transplantation of a hand or face that includes multiple tissue types such as nerve, muscle, and bone. VCA recipients must remain on lifelong immunosuppression to prevent transplant rejection.

Researchers at the University of Pittsburgh and Wake Forest University received an FY 2014 award to better understand the interactions of different VCA tissue types with the immune system (Aral et al., 2021). By computational and statistical analysis of 27 proteins known to mediate the inflammatory process, the team was able to develop maps of the key immunological processes driving the immune response following VCA in a rat model. These inflammatory network maps were developed for skin and muscle samples individually and then combined with the analysis of peripheral blood samples to develop an in silico (virtual) animal model. This analysis suggests a complex inflammatory interaction after VCA in the presence of immunosuppression and identified the protein leptin as a key driver of the immune response.

This work can help identify markers for early detection and targeted treatment of acute rejection for those Service members who may benefit from a VCA to restore function and quality of life after traumatic injury.

This effort was supported by the Reconstructive Transplant Research Program with program interest from the Combat Casualty Care Research Program/Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Utilization of Simple Walking Model to Optimize Transfemoral Prosthesis Limb Stability

A research endeavor at Northwestern University is expected to have a future impact on the prosthetics field by creating new numerical models to simulate transfemoral prosthetic gait. These models have the potential to help inform future investigations on interactions between commercially available prosthetic components that are used clinically to build prostheses. Additionally, developing new numerical models will help generate new Clinical Practice Guidelines (CPGs) for transfemoral prosthesis design. CPGs are common healthcare instruments that provide recommendations for optimizing interventions using evidence-based practice. Currently, CPGs exist for individual prosthetic components (feet or knees) but do not have enough research evidence to shed light on interactions between the combinations of prosthetic knees and feet. The mechanical performance of a transfemoral prosthesis is influenced by both the knee and feet components, which can alter the stability and functionality of the prosthetic knee and ultimately impact the user.

The overall goal of this research project is to systematically compare different combinations of mechanical prosthetic knee joint and foot components to determine how walking and standing performance are affected. The aim of preliminary studies is to inform transfemoral prosthesis design by using a simple gait model to investigate the interacting effects of prosthetic knee alignment and foot stiffness on prosthetic knee stability during the stance phase of gait, where the entire body weight of the user is loaded onto the prosthesis. Published preliminary results (Pace, Howard, Gard, & Major 2020) utilized a simple walking model, based on an inverted pendulum design, to simulate single limb support biomechanics. Several conditions were adopted in creating the simple numerical model to specifically assess single limb support during the stance phase of gait. The preliminary results suggest that there is a solution space within the model that contains certain combinations of knee alignment and foot stiffness that guarantees the most knee stability in single limb support. These preliminary results could lead to informing prosthetists about optimized knee and feet combinations for their patients.

Further work of this group includes creating a more sophisticated predictive stance phase model as well as a swing phase model for prosthetic transfemoral gait. The overall expectation from this project is to develop new numerical models that will help make significant progress in providing the best optimized transfemoral prosthesis design to Service members, Veterans, and civilians as they return to normal daily function.

This effort was supported by the Orthotics and Prosthetics Outcomes Research Program with program interest from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Photo credit: Petty Officer 3rd Class Aaron La/ U.S. Navy

Agonist-Antagonist Myoneural Interfaces Augment Volitional Motor Control and Restore Proprioception After Lower-Extremity Amputation

Traditional amputations disrupt the dynamic way muscles work together to move a limb. This uncoupling produces abnormal signaling between the muscles and the brain, and patients lose proprioception, the ability to perceive where their limb is in space without looking at their limb. Advancements in myoelectric prosthetic knee and ankle technologies have been significant, yet patients with lower-extremity amputation still experience limits in their ability to provide independent control signals for these devices. A person with an amputation could more fully take advantage of the advanced myoelectric prosthetic devices if they had dynamic coupling of the residual muscles and greater proprioception.

An FY16 Peer Reviewed Orthopaedic Research Program award to Brigham and Women's Hospital (BWH) titled "A novel approach to lower-extremity amputation to augment volitional motor control and restore proprioception" brought together the surgical skills from researchers at BWH with the prosthetic expertise of researchers at Massachusetts Institute of Technology. The team's scientific approach allowed them to reimagine the way a traditional lower-extremity amputation is performed. The new surgical technique, Agonist-Antagonist Myoneural Interface (AMI), surgically preserves and relocates the peripheral nerves and links pairs of muscles that would normally work in an agonist/antagonist way in an intact limb. The surgical linkage of these muscle pairs means that when one muscle contracts, the other is stretched.

A comparison of 15 subjects with a below the knee (BKA) AMI procedure to seven subjects with a traditional BKA procedure showed a positive outcome for the new surgical technique. The BKA AMI subjects experienced greater control of the musculature in their residual limb, produced more differentiable control signals for myoelectric prosthesis use, and demonstrated greater precision of movement than the subjects with

a standard BKA procedure. The AMI procedure provides the benefits of proprioception and phantom limb perception. Comparison of three above the knee (AKA) AMI subjects to three BKA AMI and three traditional AKA subjects showed similarly positive outcomes. The AKA AMI procedure preserved the signals for the knee, ankle, and subtalar joints, enabling the patient to control different aspects of their prosthetic limb. The production of distinctive signals from the paired musculature and the related nerves allows high fidelity neuroprosthetic control of the myoelectric limb.

This study has been performed in a small number of subjects, and further investigation may continue to provide opportunities for refinements. The innovative AMI procedure shows promise as a new way to provide improved outcomes and increased myoelectric control of prosthetic devices for people with amputations. Perhaps in the future, the positive outcomes of the AMI procedure will require that myoelectric prosthetic devices be improved to better match the increased capabilities of the new architecture of the musculature and peripheral nerve placement within the residual limb.

This effort was supported by the Peer Reviewed Orthopaedic Research Program with program interest from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Grade 1 Rejection in Human Face Transplant Recipients is Not Pathological

At least 40 human face transplants have been performed worldwide, and this reconstructive option can be life-transforming for traumatically injured Service members and civilians. Transplant recipients must remain on lifelong immunosuppression to prevent rejection of the transplanted allograft. Even with an immunosuppression regimen, most face transplant recipients experience at least one episode of acute rejection during the first year after transplant.

A team at Brigham and Women's Hospital received an FY17 award from the Reconstructive Transplant Research Program to better understand the biological processes underlying acute rejection in face transplant recipients (Wins et al., 2021). The team studied skin biopsy samples from seven face transplant recipients and completed gene expression profiling, immunostaining, and high-throughput sequencing of non-rejecting (Grade 0) through to Grade 3 severe-rejection. It was discovered that there are no significant differences in gene expression between non-rejection (Grade 0) and mild-rejection (Grade 1) and no differences in the number of T cells between these same samples. This suggests that Grade 1 rejection does not represent a pathologic state, and based on this finding, the team has discontinued treating mild rejection in their face transplant recipients, a substantial change in clinical practice.

This effort was supported by the Reconstructive Transplant Research Program with program interest from the Combat Casualty Care Research Program/Joint Program Committee-6 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Secondary Injury and Comorbidities

Health Conditions Among Special Operations Forces Versus Conventional Military Service Members

Researchers at the TBI Center of Excellence and James A. Haley Veterans' Hospital conducted a study comparing TBI characteristics and comorbid medical profiles of Special Operations Forces (SOF) and Conventional Forces (CF) who sought care at a U.S. Department of Veterans Affairs Polytrauma Rehabilitation Center. The study included 157 SOF personnel and 365 CF personnel. The study found SOF personnel exhibited demographic, service history, and injury differences, including notably higher number of blast injuries than the CF cohort. This finding likely reflects differential exposure to blast overpressure, which is characteristic of SOF training and operations. SOF personnel also had a higher number of comorbidities.

This study was funded by the U.S. Department of Veterans Affairs TBI Model Systems Program of Research, Veterans Health Administration Central Office.

The Effect of Low-Level Repeated Blast Exposure on Long-Term Respiratory Health and Lung Pathology

Several epidemiological research studies have identified the risk associated with blast overpressure exposure and pulmonary deficits in Service members and Veterans. Cardiopulmonary symptoms such as shortness of breath and decreased exercise tolerance after return from deployment are a major concern for many Service members and Veterans of the conflicts in Iraq and Afghanistan. While mild TBI has been a major focus of long-term health effects, these same individuals (n = 300,000–450,000) may have experienced subclinical blast lung injury, partially explaining cardiopulmonary symptoms and dysfunction after deployment. Comprehensive studies to understand long-term, chronic effects of blast-related lung injury are particularly lacking. The goal of this study is to understand the long-term pulmonary deficits associated with repeated low-level blast exposure in the absence of any gross lung injury, using functional and pathological studies. Preliminary data from the pulmonary function test showed persistent changes in function following repeated blast exposures (four times at ~8.5 psi), specifically, persistent changes in end expiratory pause (EF50) and expiratory and relaxation times, while enhanced pause was decreased. Complementary to the data from the pulmonary function test, immunohistochemistry data revealed the potential onset of fibrotic processes (such as increased alpha-smooth muscle action and tumor growth factor-beta) following four blasts at ~8.5 psi, when compared to shams, at one-month post-blast. Several additional analyses are currently underway to assess blast exposures of four and fourteen times, up to three months post-blast. A parallel clinical study is being conducted by the Department of Veterans Affairs in New Jersey and Houston, Texas.

This research was supported by the Peer Reviewed Medical Research Program.

Environmental Sensors in Training Program Occupational Repetitive Blast Exposure: Immediate, Acute, and Longitudinal Effects

A growing body of literature suggests that repeated low-level blast exposures, such as those that occur in some military training, coincide with measurable, yet transient, effects on the brain without concomitant diagnosed injury. Further, chronic exposures to such military training are associated with cumulative effects on the brain that may correspond to injury that are not currently recognized as such. In FY22, the Walter Reed Army Institute of Research (WRAIR) will complete a series of studies, in conjunction with routine training, to support evidence-based decisions regarding blast exposure effects, monitoring feasibility, and health and performance risk assessments. These studies characterize personnel exposures from a variety

of weapon systems/environments ranging from low overpressure (less than 4 psi) to moderate overpressure (4–8 psi) and investigate neurocognitive performance, symptom reporting, hearing ability, and physiological responses, including eye tracking effects and blood-based proteomic and epigenetic biomarkers for neurotrauma. Data are collected less than five minutes after blast exposure, at end of day, and, where available, longitudinally across years with the instructor cadre. Participation is active, with over 750 enrolled research volunteers at more than 20 sites. Participants have been exposed to low-level blast from heavy wall breaching, .50 caliber rifle, .50 caliber machine gun, artillery, grenades, flashbangs, and shoulder-launched munitions, including the Gustaf recoilless rifle. Research program data demonstrate that current calculations for minimum safe distance can be inaccurate in complex environments. Also, in addition to blast overpressure, high-level sound pressure exposures, including very low-frequency sound (infrasound, below 16 Hz), appear to be a key component of risk in these environments. As of July 2020, these exposures recorded by WRAIR are available to be included in individual Service member official records in the Defense Occupational and Environmental Health Readiness System – Industrial Hygiene. Cognitive deficits identified immediately after blast exposure resemble those observed in the study of concussion with the U.S. Military Academy boxing program, and this behavioral response has an association with exposure "dose." Changes in blood-based neurotrauma biomarker levels, eye tracking performance, and binaural hearing ability and in surrogate brains also have association to blast exposure, further suggesting a potential dose-response relationship. Environmental Sensors in Training (ESiT) epidemiological studies suggest that chronic blast exposure has associations with clinical outcomes of diagnosed tinnitus and vulnerability to post-concussion syndrome. The ESiT program provides critical information for understanding occupational blast exposure and associated neurological and physiological effects. Results are an asset for risk/benefit assessment; they also aid in developing detection and mitigation strategies for Service members in combat and training environments and have been used by multiple training units to develop methods to reduce exposure while preserving training quality and Service member lethality. WRAIR staff and collaborators publish findings in peer-reviewed medical research literature and, in coordination with the Defense Health Agency, share research program data with multiple DOD institutions. Several notable publications have resulted from this work in FY21: *JAMA Network Open* (Boutté et al., 2021); *Frontiers in Molecular Neuroscience* (Chatterton et al., 2021); *Military Medicine* (Medda et al., 2021); *Military Medicine* (Przekwas et al., 2021).

This work was sponsored by the U.S. Army Medical Research and Development Command Military Operational Medicine Research Program, Joint Program Committee 5, and the Defense Health Agency.

Outpatient Opioid Prescriptions Among Service Members Who Sustained Combat-Related Amputations in Iraq and Afghanistan Conflicts

Researchers at Naval Health Research Center examined patient characteristics associated with outpatient opioid prescriptions during the first year post-injury for 1,638 Service members who sustained major limb amputation(s) in Iraq and Afghanistan from 2001 to 2017. Race (White versus other), number of limb amputations, lower limb amputation (versus upper limb), infection, chronic pain, and posttraumatic stress disorder predicted higher opioid prescription dosages. Traumatic amputation (versus delayed more than 24 hours post-injury) and TBI predicted lower opioid prescription dosages. Blast injury did not predict opioid prescription dosage measures.

The study results can inform rehabilitation planning and opioid prescription practices

alongside DOD and U.S. Department of Veterans Affairs clinical guidelines. These results apply to opioid prescriptions only, as patient opioid consumption was not measured and may vary.

This effort was funded by the DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE) and the U.S. Navy Bureau of Medicine and Surgery's Wounded, Ill, and Injured Program.

Symptom Profiles Following Combat Injury and Effects on Long-Term Quality of Life

Little research exists on how symptoms reported in the initial phase post-injury relate to long-term quality of life. Investigators at Naval Health Research Center examined 885 military personnel who were wounded during combat operations (89 percent of injuries caused by blasts) and completed a post-deployment health assessment where symptom information was collected (MacGregor et al., 2021a). Participants responded to a quality of life survey years later. Symptom profiles of multi-morbidity, psycho-cognitive, and musculoskeletal were predictive of lower long-term quality of life. These findings may inform clinical care following combat injury.

This effort was supported by the U.S. Navy Bureau of Medicine and Surgery.

The Relationship Between Blast-Related Hearing Threshold Shift and Insomnia in U.S. Military Personnel

Service members are at a more significant risk for hearing loss and insomnia due to the high-risk environment the battlefield poses for auditory system damage, thus creating public health problems. The goal of this research was to address gaps in understanding the association between hearing loss and insomnia. A recent study (MacGregor, Joseph, Markwald, & Doughtery 2021) investigated the association between hearing loss and insomnia by examining 652 Service members who were injured by a blast during combat operations. Service members were identified through the Blast-Related Auditory Injury Database. The researchers analyzed audiogram data of those who had medical records indicating a diagnosis of insomnia. Findings indicated those with hearing-threshold shift (i.e., an early indicator of hearing loss) were more likely to be diagnosed with insomnia than those with normal hearing. This was the first study to identify an association between significant threshold shifts and insomnia. These findings suggest that interdisciplinary care may be needed for Service members and Veterans experiencing both hearing loss and insomnia, and it is recommended that audiologists collaborate with sleep medicine and mental health workers to manage patients with this combination. This work was published in Military Medicine and supported by the Naval Health Research Center, Illinois State University, and Leidos.

This work was funded by the U.S. Navy Bureau of Medicine and Surgery under work unit No. 60808.

PTSD-Screening Tool Program

The U.S. Army Medical Materiel Development Activity (USAMMDA) Warfighter Brain Health (WBH) Project Management Office (PMO) established a program to develop objective monitoring, screening, diagnostic, prognostic, and predictive tools related to identification, triage, treatment, and prevention of behavioral health issues in Service members from pre-Role 1 through the Role 4 in deployed and garrison environments. Currently, behavioral health issues are only detected through self-report or an observed decrease in functioning. Objective behavioral health tools, which do not rely on subjective assessments, are designed to help Commanders, combat operational stress control teams, and medical providers more quickly identify and help Service members in need. The objective behavioral health tools capability will help providers better respond to comorbidities of blast and other traumatic combat exposures.

This program is funded by the Defense Health Agency.

Photo credit: 1st Lt. Ryan DeBooy/ U.S. Army

Addressing the Physical and Mental Health of Female Service Members Injured on Combat Deployment

Sex- and gender-based health disparities have been well documented in the literature and may be of special concern for female Service members. Most research in this area has prioritized objective medical records at the expense of patient-reported outcomes. Researchers from the Naval Health Research Center examined physical and mental health-related quality of life, mental health symptoms, and health behaviors among 230 female Service members injured on deployment, of whom 70.2 percent (160) were injured in a blast. Results indicated that about half of injured female Service members screened positive for a mental health condition. This group also evidenced risky health behaviors including problematic drinking, poor sleep, and physical inactivity. Most mental and behavioral health factors were interrelated. Results from this research provide additional evidence for the importance of access to integrated and effective mental health care treatment for injured female Service members. The results also indicated the need for screening in health care settings that address the multiple factors (e.g., mental health symptoms, alcohol use, poor sleep) that may lead to poor outcomes. This work was published in the International Journal of Environmental Research and Public Health (Watrous et al., 2021).

This research was sponsored by the U.S. Navy Bureau of Medicine and Surgery.

A Study from the Wounded Warrior Recovery Project Examining Health Behaviors Among Service Members Injured on Deployment

Much evidence exists describing long-term health problems among injured Service members, but little research has described the specific health behaviors injured Service members engage in. Researchers at the Naval Health Research Center investigated these specific health behaviors. Participants were 3,303 injured Service members who completed a behavioral health assessment between September 2018 and April 2019. About half of participants (49 percent) screened

positive for posttraumatic stress disorder and/or depression. Participants reported inadequate sleep and poor sleep quality, high rates of alcohol use and problems, cigarette, and tobacco use, and low levels of physical activity. These findings indicate a continued need to refine in-theater concussion rehabilitation. With two exceptions (number of drinking days and tobacco use), participants who screened positive for a mental health concern reported worse health behavior outcomes. To promote health and wellness, results underscore the importance of examining the interplay between behavioral health and mental and physical outcomes among wounded warriors. This work was published in Military Medicine (McCabe, Watrous, & Galarneau, 2021).

This research was supported by the U.S. Navy Bureau of Medicine and Surgery.

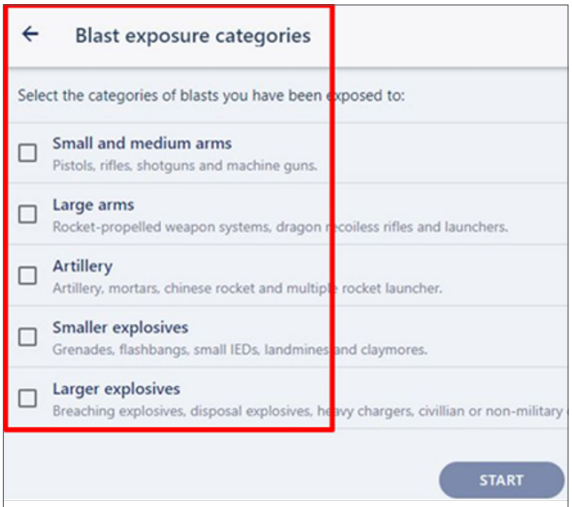
Toward a Joint DOD Blast Exposure Surveillance System

The Naval Health Research Center (NHRC) has established a translational program of research evaluating blast exposure and its multi-dimensional health effects in military personnel. In one of several FY21 publications, researchers evaluated the relationships between combat exposure, blast exposure, and sympathetic nervous system (SNS) responses to maximal exercise stress in male explosive ordnance disposal operators. During acute exercise, individuals with more substantial combat exposure and those with blast exposure demonstrated blunted electrodermal patterns (a surrogate marker of SNS activity) in comparison to their low/non-exposed counterparts. These findings may imply that such exposures are linked to suboptimal SNS function and enhance overall knowledge of factors influencing resilience.

In another report, researchers evaluated the effects of combat and blast exposure on mental health (positive and negative). The team observed that self-reported involvement in a vehicle crash/blast was generally associated with negative mental health symptoms. However, preliminary evidence of "stress inoculation" was found via other military-related stressors, indicating that greater combat exposure and deployments protected against the deleterious effects of blast on mental health. Building upon prior gene-environment work (blast exposure interacts with a serotonin genetic variant [5-HTTLPR] to predict posttraumatic stress symptoms), researchers are currently evaluating the influence of blast exposure and stress-related genetic variants on behavioral health symptoms in a large sample of Naval personnel. Preliminary data indicate there are combined effects of glucocorticoid receptor polymorphism (Bcl-1) and vehicle crash/blast involvement on negative behavioral health. As an exploratory project, the research team is currently examining the effects of blast exposure on telomere length and how selected genetic variants may act as moderators in that relationship. Telomere shortening is an indicator of biological aging and may be a surrogate marker of physiological weathering, due to chronic disease and stressful life events. Altogether, these findings are anticipated to have implications for programming, policy, and/or clinical practice, and this body of work continues to transition toward a Joint DOD Blast Exposure Surveillance System (BESS).

In collaboration with the Neurotrauma Department at Naval Medical Research Center, researchers translated the Blast Exposure Threshold Survey (BETS) (Modica et al., 2020) into a mobile application (app) named "Blast App 1.0" (Figure 7-15). In the near term, the app can be used to determine blast exposure profiles for different military occupations which can, in turn, help to establish community-specific safety standards. The app is currently undergoing beta testing, and BETS past activities, findings to date, and next steps (ongoing and envisioned) for the BESS have been presented to the TBI Center of Excellence Division Chief and Section 734 Working Group. Future versions of the Blast App will include

FIGURE 7-15: Screenshot of "Blast App 1.0"



Screenshot of the "Blast App 1.0" mobile application which was adapted from Modica et al., 2020 (https://doi.org/10.1089/neu.2020.7405). Five primary exposure categories are used to estimate lifetime blast exposure.

risk stratification, evidence-based symptom inventory, and a personalized user experience (e.g., recommended readings, curated resources, targeted interventions). The goals of a Joint DOD BESS are to memorialize lifetime blast exposure in Service members, fully characterize the complex, multi-faceted associations between blast exposure and health outcomes, and serve as a decision support and clinical tool. Resulting work from this research was published in *Military Medicine* (Barczak-Scarboro, Hernández, & Taylor, 2021) and *Stress and Health* (Taylor, Barczak-Scarboro, Laver, & Hernández, 2021).

This project was supported by the Defense Medical Research Development Programs' Clinical Research Intramural Initiative Military Optimization Research Award, work unit no. N1906, and by the Joint Program Committee-5 Development of Exposure Standards to Repeated Blast Exposure Program, work unit no. N1909.

Multi-Disciplinary Approaches Toward the Restoration of Function Following Volumetric Muscle Loss

Volumetric muscle loss (VML) resulting from combat-related trauma or secondary to surgical procedures presents pervasively throughout the Military Health System. It is a leading factor in the decision to amputate, with 80 percent of the surgical amputations performed on Service members directly related to missing skeletal muscle tissue. Historically, chronic functional deficits following VML were considered a part of the natural and unavoidable sequelae of injury, and thus VML injuries often went without a definitive treatment due to a lack of effective acute care therapeutics. Subsequently, these injuries followed a fibrotic repair paradigm leading to persistent muscle weakness and long-term disability. To address this unmet need, researchers have established a multi-disciplinary, focused research effort to develop and evaluate a myriad of putative acute care interventions (e.g. small molecules, biologics, biomaterials) and synergistic, multi-modal treatment strategies (e.g., Regenerative Rehabilitation) to find a near-term solution capable of restoring end organ function of musculature affected by VML.

This research resulted in the publication of a manuscript describing the effects of licofelone, a dual-action anti-inflammatory drug, on VML wound healing outcomes, in conjunction with a biologic scaffolding in a rat VML model. Licofelone is efficacious for damping pro-inflammatory transcriptional markers in the wound bed, which is correlated with a modest reduction in Type I collagen content. This biological outcome, however, was not coupled with a meaningful effect on neuromuscular function. These findings suggest that moving forward, efforts related to modulating the wound healing environment of VML should focus on polypharmaceutical strategies that target multiple aspects of the early pathophysiology of VML in order to provide an environment sufficiently permissive for local

regenerative therapies to promote restoration of myofiber number. This research was published in *Cell Tissue Research* (Goldman, Janakiram, Valerio, & Dearth, 2021).

Throughout FY21, the research team continued to evaluate the efficacy of a semi-synthetic injectable hydrogel as an acute care therapeutic in a translational porcine VML model and candidate material systems for maintaining and stabilizing the VML wound environment for prolonged field care applications. The team received two new awards to include 1) an award from the United States Army Medical Research and Development Command (USAMRDC) to investigate a potent immunomodulatory biologic on functional wound healing outcomes of VML in conjunction with minced muscle autografts; and 2) an award from USAMRDC to evaluate a dual anti-fibrotic and pro-regenerative strategy to facilitate improved functional outcomes in the treatment of VML.

These efforts were conducted within the Uniformed Services University of the Health Sciences by investigators from the DOD–VA Extremity Trauma and Amputation Center of Excellence (EACE) and received support from the U.S. Army Medical Research and Development Command through the Peer Reviewed Medical Research Program and the Orthopaedic Trauma Association.

Factors Associated with Diagnosis of Disruptive Dizziness Following Deployment-Related TBI

Disruptive dizziness is one of many ongoing symptoms experienced by Service members after blast exposure. Dizziness measures are subjective and often related to comorbidities, making it challenging to diagnose and treat. Many variables affect the level of care each patient receives. With funding to the James H. Quillen Veterans Affairs Medical Center (Mountain Home, Tennessee) and the George Wahlen VA Medical Center (Salt Lake City, Utah), researchers have analyzed the frequency of disruptive dizziness in post-9/11 Veterans with deployment related TBI, as well as factors associated with dizziness or vestibular diagnosis (DVD) (Swan et al., 2021).

Retrospective data were collected from 126,365 post-9/11 Veterans with deployment related TBI, with more than 15 percent having experienced disruptive dizziness. Several factors were found to be associated with diagnosis of dizziness. Access to, or use of, specialized care was the best predictor of DVD. Other factors include race and diagnosis of substance use. Mental health disorders, cognitive dysfunction, headache, and auditory problems were associated with increased rate of DVD. As some of these conditions may be treated with psychoactive medications, dizziness may be related to these conditions as a side effect of medication.

The outcomes from this study will be important when considering the management of dizziness symptoms and creating improved access to care. Ongoing care from clinicians with specialty training in the vestibular system will likely contribute to accurate diagnoses of dizziness, as well as increased patient education and cultural competency in health disparities. Taken together, these data will contribute to evidence-based clinical pathways for the treatment of disruptive dizziness following TBI.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Assessment of Photosensitivity in Veterans with Complex TBI

Researchers at Oregon Health and Science University–Portland conducted a study to quantify photosensitivity in Veterans with complex TBI and, using functional brain imaging, test whether a dim light stimulus can activate pain-related brain areas in Veterans with complex TBI (Elliot et al., 2021). The study examined 200 Veterans recruited within the U.S. Department of Veterans Affairs Portland Health Care System, each of whom was evaluated for TBI using three methods: self-report, electronic medical record, and a structured clinical interview. Participants also completed validated questionnaires assessing chronic symptom severity in broad health-related domains (pain, sleep, quality of life, and post-concussive symptoms), which allowed an assessment of whether functional outcomes depended on the method used to determine the presence or absence of TBI. This work could provide insight into the mechanisms of chronic pain in complex TBI.

The team found that different methods varied in sensitivity for detecting a prior TBI, with the rate of diagnosis quite different depending on the method. This analysis has two important implications. First, understanding the exact methods used to ascertain TBI is essential when interpreting results from any study, given that results and conclusions may differ dramatically depending on the method. This issue will become even more critical when interpreting data merged from multiple sources within centralized repositories (e.g., Federal Interagency Traumatic Brain Injury Research [FITBIR]). Second, the combination of methods identified the group that could be considered "symptomatic" TBI, with severe chronic symptomology. This suggests that development of a composite measure that includes self-report, medical status, and neuropsychological assessment elements would be an important next step for the field and would allow researchers and clinicians to focus on the group with the greatest scientific interest and clinical need.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Development of Objective Measures of Turning to Improve Return to Duty Assessment

To protect the safety of Service members and their units, it is critical to make appropriate return to duty decisions after mild TBI (mTBI). These decisions have historically been based on self-reported symptoms, standardized physical or cognitive tests, or objective measures of a single system, which may be insensitive or lack ecological validity for the demands of military activities and daily life. On the other hand, complex tasks like dual-task paradigms and ambulatory turning can provide valuable information about functional deficits after mTBI. Successful turning relies on integration between vestibular (balance), vision, somatosensory, motor, and cognitive systems to plan for movement of multiple parts of the body. Advances in wearable sensors have made it possible to collect objective, robust, reliable, and sensitive assessments of turning performance in a non-laboratory setting.

A team at Oregon Health and Science University is exploring the value of dual-task turning measures for clinical assessments and return to duty decisions after mTBI. They have previously reported that individuals with mTBI show impairments in turning performance; now, they are determining the best task and outcome measure for return to duty decision based on diagnostic accuracy, predictive capacity, and responsiveness to rehabilitation. As part of this effort, they are investigating which measures are reliable across clinical and research sites, which is critical for any

assessment that will be widely used in practice. In a recent publication (Parrington et al., 2021), the team tested healthy young adult volunteers from two different sites on the same turning tasks while fitted with wearable sensors. Of the 21 outcomes they measured, none were statistically different between sites. Six were statistically equivalent, meaning certain tasks may be better suited for multi-site studies.

Furthermore, sensors at the pelvis and trunk regions were more equivalent between sites than sensors at the head, potentially due to differences in the visual environment. These results provide valuable information about which tasks and outcomes to investigate further in active-duty Service members as they undergo rehabilitation for mTBI. This project will provide more accurate testing of symptoms and new tools for clinical decisions in individuals with mTBI that can be generalized and adopted into military and civilian treatment settings. Improved return to duty decision-making will improve mission readiness and safety for Service members.

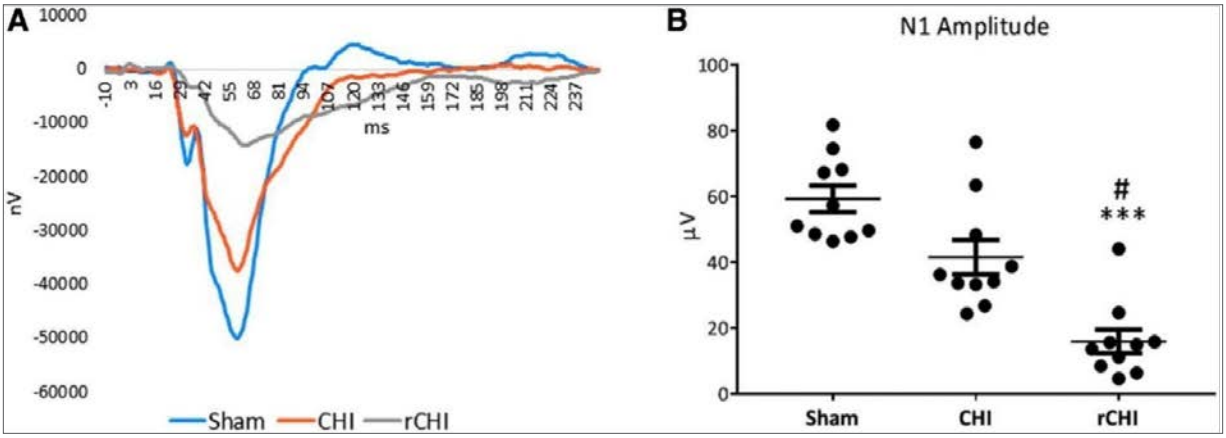
This effort was managed by the Congressionally Directed Medical Research Programs with support from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

CHIMERA-Induced Rotational Injuries Alter Visual Functions

Investigators at the Uniformed Services University of the Health Sciences (USUHS) continue to have a keen interest in the neuropsychiatric consequences of TBI, including changes in fear and anxiety (Kostelnik et al., 2021; Tucker and McCabe, 2021). Among the factors that have been considered is the impact of impact-rotational injuries on performance in the areas of memory and sensory function. Researchers at National Institute on Alcohol Abuse and Alcoholism (NIAAA) have employed Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA) in mice that sustained one or three head injuries (Desai et al., 2020). Testing with the Morris water maze indicated impairments, which traditionally would be considered solely a sign of memory impairment. However, further testing indicated visual system impairments where mice also performed worse on a visual cliff task and exhibited a reduction in N1 visual evoked response — particularly mice that sustained multiple injuries. Histological analyses confirmed there was significant neuropathology in the optic tract following acceleration injury (See Figure 7-16 for analysis).

This work was conducted at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Rockville, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine and the NIAAA Intramural Research Program.

FIGURE 7-16: Mice with multiple TBI showed impaired visual evoked potential pattern.



CHIMERA-Induced Rotational Injuries Impair Hippocampus-Related Cognition

Researchers at the Uniformed Services University of the Health Sciences (USUHS) continued to employ Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA) while focusing on hippocampal memory (Tucker et al., 2021). Performance on the Morris water maze was impaired, but testing indicated a component of the performance deficit was due to optic tract injury. This group employed a second behavioral test, trace fear conditioning, and found there was impairment on this task, which is attributed to hippocampal function (Figure 7-17). Their findings matched the hippocampal pathology reported after blast by Nonaka et al. (2021). Deficits in fear conditioning indicates damage to the basic neurological circuits for fear learning, which are relevant to neuropsychiatric symptoms, including TBI-related fear and PTSD. The models lend themselves to understanding the basic neurochemistry of fear as well as translational, pharmacological studies for therapeutics.

This work was conducted at the Uniformed Services University of the Health Sciences (Bethesda, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine (grant nos. 65310-309-6.01 and 65310-310185-6.01).

Long Term Clinical Correlates of TBI: Imaging, Biomarkers, and Clinical Phenotyping Parameters

A natural history study is being conducted at the National Institutes of Health (NIH) Clinical Center in coordination with the Center for Neuroscience and Regenerative Medicine (CNRM). The study follows a cohort of participants with a clinical diagnosis of non-penetrating TBI. Participation in the TBI cohort study includes up to nine evaluation sessions (at 30, 90, 180, and 365 days after injury), then once per year until year five. Evaluations included neuroimaging via non-contrast magnetic resonance imaging, neuropsychological evaluations, other functional evaluations, blood and urine collection; and auditory, vestibular, and oculomotor assessments. Healthy volunteers and TBI patients are scheduled, as needed, to match assessments. Healthy volunteers were also studied to provide multiple CNRM investigators with hematological, cognitive, and functional outcome measures and neuroimaging parameters to compare to participants with TBI.

A recent publication (Flynn et al., 2021) investigated a unique way of quantifying proteins found in peripheral blood of patients with TBI. Continuing the investigation into blood biomarkers work done in FY20, which used serum or plasma

FIGURE 7-17: Brain injury induced by repeated CHIMERA also affected cognitive performance as assessed by trace fear conditioning in separate mice on days 24–26 following the final injury.

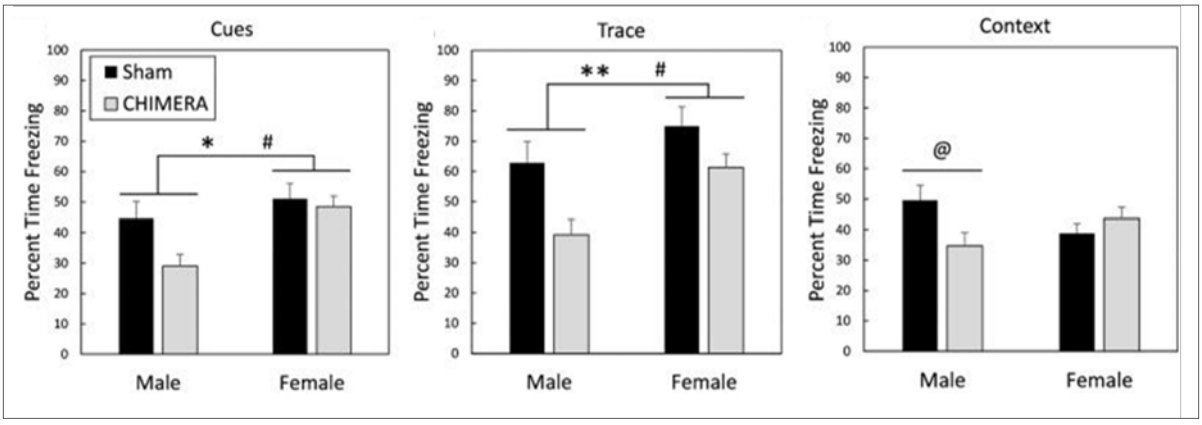


Photo credit: Cpl. Scott Jenkins/ U.S. Marine Corps

protein detection for evidence of injury as early as 30 days post-injury, the study team this time quantified proteins found in the extracellular vesicles (EVs). EVs are found in eukaryotic fluids, carry cargo to and from all areas in the body, and can protect their contents from degradation by proteases or ribonucleases that are common in blood. Not only are EVs suggested to be more biologically active than proteins found in blood they can transverse the blood-brain barrier and be isolated from peripheral biofluids, making them a promising new avenue of investigation for central nervous system functioning and the development of TBI biomarkers.

Findings from this publication suggest that blood-derived EV concentrations with certain blood-based biomarkers, drawn as late as one year after injury, are higher in patients with a reported TBI when compared to controls. Additionally, these elevations relate to injury severity and poor recovery outcomes, suggesting that TBIs may alter the activity of these biomarkers, likely contributing to individual variability in recovery.

This longitudinal study has provided unique insights into the correlation of many behavioral, physiological, and cognitive factors associated with TBI. Additional analyses from this patient cohort will expand on these associations and inform future research in the prevention and treatment of TBI.

This research was funded by the Intramural Research Program at the National Institutes of Health and Center for Neuroscience and Regenerative Medicine.

Blast TBI's Effect on the Limbic-HPA Axis PI

Service members are at a greater risk of experiencing blast (b)TBI. Returning Veterans with mild blast TBI (mbTBI) are increasingly diagnosed with co-morbid disorders such as PTSD. When exposed to TBI, women are more likely than men to have a poorer outcome and develop PTSD. The sexually dimorphic hypothalamic-pituitary-adrenal (HPA) axis is the major neuroendocrine regulator of the stress response. Current literature

shows a dysregulation of the HPA axis after mTBI. The overarching goal of a recent study is to understand short- and long-term sex-dependent neurobiological consequences that result in the increased risk of anxiety disorders associated with mbTBI. The study has three aims: 1) Determine if TBI causes long-term changes in HPA axis through programmed cell death and gene expression in the stress circuitry, 2) Determine if TBI causes morphological changes in prefrontal cortex (PFC) neurons that project to the paraventricular nucleus (PVN), and 3) Determine fear-related behavioral outputs associated with limbic regions that regulate the HPA axis stress response after mbTBI.

The behavioral response to stress is controlled by the neurocircuitry of the limbic-HPA axis. The limbic neurocircuitry provides both direct and indirect inhibitory input to the PVN which, in turn, integrates this information to induce a neuroendocrine behavioral response. Within this neurocircuitry, the PFC, hippocampus, and amygdala, are crucial for the formation and extinction of fear memory. This proposal first focuses on the PFC because it is the top-down controller of the other subcortical regions.

PFC activation disinhibits the corticotropin-releasing factor neurons in the PVN via direct projections or indirect projections to enhance the stress response. This study has submitted three manuscripts for publication and has been presented at several events.

This work was presented at the Uniformed Services University of Health Sciences/ National Institutes of Health Traumatic Brain Injury Research Consortium (Fall 2020) due to the cancellation of the 2020 Military Health System Research Symposium. This presentation covered "Chronic Variable Stress Worsens Effects of Mild Blast Traumatic Brain Injury" and "Increased Sensitivity to Ketamine's Behavioral Effects in Mice Exposed to Mild Blast-Induced Traumatic Brain Injury." This research was also presented at American University (Fall 2020); the 2021 Women in Combat Summit-Forging the Future: How Women Enhance the Fighting Force; Auburn University (Spring 2021); National Neurotrauma Society panelist: Sex Differences in TBI Research; Center for Neuroscience and Regenerative Medicine seminar (June 2021); and Walter Reed Army Institute of Research (Fall 2021).

This work was funded by the Center for Neuroscience and Regenerative Medicine.

Prolonged Care

Mental and Physical Health, and Long-Term Quality of Life Among Service Members with Extremity Injuries

Service members with extremity injuries or TBI may be at risk for long-term deficits in physical and mental health functioning compared to Service members with other injuries. Researchers at the Naval Health Research Center combined medical records with patient reports of mental health- and health-related quality of life (HRQOL) for 2,537 injured Service members, of whom 76 percent (1,928) were injured in a blast. This study showed that injury type was indirectly related to long-term HRQOL via its associations with physical health complications and mental health symptoms. Specific treatment plans and rehabilitation efforts are needed to address secondary physical and mental health conditions and to promote readiness, health, and overall wellness of injured Service members. This work was published in Health and Quality of Life Outcomes (McCabe, Watrous, Eskridge, & Galarneau, 2021).

This research was funded by the U.S. Navy Bureau of Medicine and Surgery.

Photo credit: Staff Sergeant Christopher S Muncy/ U.S. Marine Corps

Virtual and Augmented Reality Technology to Treat Symptoms of Vestibular Injury

Service members who are injured as a result of blast exposure often experience multi-faceted, persistent symptoms. Vestibular dysfunction is part of this sequelae and can manifest through auditory and visual impairments, gait abnormalities, and cognitive deficits, which may impact fitness for duty. Dynamic and customized vestibular rehabilitation programs using virtual reality (VR) have previously been developed and validated using the Computer Assisted Rehabilitation Environment (CAREN), a large-scale VR-based system. Despite the benefits observed by both clinicians and patients, there is limited access to CAREN systems. To increase accessibility and meet the clinical demand for mobile vestibular rehabilitation tools, the Naval Health Research Center and the National Intrepid Center of Excellence collaborated with a team of therapists to develop a host of software applications that can be utilized on an augmented reality (AR) head-mounted display device, as well as the CAREN. These applications include a battery of vestibular tasks (e.g., balance, gaze stability, visual scanning) with settings that can be individualized to meet specific patient needs and achieve functional goals. Outcomes have been developed for each task, and the software also allows for integrated physiological monitoring (e.g., eye-tracking, heart rate monitoring, kinematics). Researchers are actively evaluating auditory and visual performance in both healthy Service members and those with mild TBI (mTBI). User feedback is also being collected. Preliminary results show congruity between outcomes collected on the AR and CAREN systems, as well as site-based equivalency. Following this comparison study, a clinical trial will be conducted to assess the efficacy of using the mobile AR system for vestibular physical therapy, by comparing pre- and post-outcomes with Service members treated on the CAREN system versus those treated with traditional vestibular physical therapy exercises. These efforts will expand the access of novel, AR-based technologies to a greater number of DOD care facilities, allowing more Service members to benefit from VR-based vestibular therapy. This research was published in Proceedings of the International Conference on Virtual Rehabilitation (Sessoms, P., Kruger, S., Delpy, K., Bodell, D., Ordek, V., Rosen, K., and VanDehy, J. Sessoms, P. [Eds.], 2021).

This work was supported under work unit number N1801 with funding through the Psychological Health and Traumatic Brain Injury Research Program, with programmatic oversight from Military Operational Medicine/Joint Program Committee-5.

Burn Survivors with Greater Than 40 Percent Burn May Continue to Military Service

This study, conducted by researchers at the Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas and University of Texas Southwestern Medical Center, aims to provide additional scientific data to policymakers, encouraging them to reconsider the current U.S. Army's Standards of Medical Fitness, Army Regulation (AR) 40-501, for recruitment and retention of burned individuals. AR 40-501 states that a "prior burn injury (to include donor sites) involving total body surface area of 40 percent or more does not meet the (fitness) standard." However, this standard comes from findings of only three studies with small sample sizes or limited methodologies.

This funded award includes studies comparing burn survivors and healthy adults, with and without simulated burns, to determine each subject's thermoregulatory capabilities. Results from this effort present data that may warrant revisiting and updating the AR 40-501 to determine the qualifications of burn survivors to serve on active duty. In particular, prior year data showed that the overall size of the individual plays a significant role in the thermoregulatory consequence of a burn injury of a given relative size: a 40 percent total body surface area (TBSA) may have less impact on a larger individual, who will have a greater absolute surface area of unburned skin to dissipate heat.

Two papers published during FY21 provide additional information on burn survivors' performance. In the first study (Belval et al., 2021), a key conclusion was that subjects with TBSA of 40 percent or greater will experience a gastrointestinal temperature (TGI) increase of more than 1 degree Celsius (compared to at rest) when exercise intensity is moderate (e.g., producing a metabolic heat generation of 6 watts per kilogram on a cycle ergometer) and the environmental condition is above ambient temperature (about 40 degrees Celsius in an environmental control chamber). However, at low exercise intensity (a metabolic heat generation of 4 watts per kilogram on a cycle ergometer) and in the same environmental condition, the increase in TGI was similar for all groups (with 0–60 percent simulated TBSA burns), sustaining under 1-degree Celsius increase in TGI. In the second study (Cramer et al., 2021), results lend support to the conclusion that attenuating sweat production, at the injury location where skin was grafted, may not be a determining factor for the overall individual's thermoregulatory capacity during exercise (e.g., treadmill walking with targeted 6 watts per kilogram of metabolic heat production in 40.1 degrees Celsius and 19.6 percent relative humidity), given that the magnitude of the elevation in core temperature was similar for individuals with simulated grafts of identical size on the torso or on the limb.

This effort was supported by the Military Burn Research Program with program interest from the Military Operational Medicine Research Program/Joint Program Committee-5 and Combat Casualty Care Research Program/Joint Program Committee-6.

Health Effects of Embedded Metal Fragments in an Animal Model

Managing shrapnel wounds may not be a new problem, but the recently recognized potential for some of these metals to be toxic may be. Metal alloys have been found to be highly toxic, causing cancer in early animal experiments. Several elemental metals are known to be cancer-causing also, and this is a concern as metal fragments can remain in the body for long durations of time. Some of these embedded metal compositions are unknown, and so the properties are unknown, as well. Researchers received an FY15 Focused Program Award to assess the health effects of blast injuries and embedded metal fragments. In one of the studies, the researchers investigated

Photo credit: Neil Adams/ U.S. Army

the health effects of embedded fragments in animals implanted with metals of toxic concern. Two papers were published as a result of the animal studies conducted. The first (Hoffman, Vergara, & Klanich, 2021) describes the effects metal fragments embedded in gatrocnemius muscle of rats have on neurological protein expression. Although few changes were observed in metal levels, a large number of synapse proteins showed reduced expression levels. The second (Hoffman, Vergara, Fan, & Klanich, 2021) looked at the effects of embedded metal fragments on urinary biomarkers of renal damage. The results showed that embedded metals were rapidly solubilized and excreted in the urine.

This effort was supported by the Peer Reviewed Medical Research Program with program interest from the Radiation Health Effects Research Program/Joint Program Committee-7.

Wearable Sensors can be Used to Assess Exercises During Vestibular Rehabilitation

Many people who experience mild TBI report acute dizziness after injury, and others experience dizziness long-term. To treat balance impairments and dizziness, patients may be instructed to perform balance and head movement exercises as part of vestibular rehabilitation treatment plan. However, there is a lack of normative data and evidence-based guidelines for vestibular rehabilitation.

Researchers at the Oregon Health & Science University and colleagues performed a pilot study to analyze the use of inertial measurement units (IMUs) that measure several aspects of balance and gait (Martini, Pettigrew, Wilhelm, Parrington, & King 2021). Twenty healthy control subjects completed vestibular rehabilitation exercises with IMUs attached at the forehead and sternum. Data collected from IMUs were used to characterize cervical and trunk range of motion and peak angular velocity during the exercises. Based on these measures, the team found that healthy adults perform vestibular rehabilitation exercise

similarly over time. Normative data was collected and analyzed for future use of IMUs.

Since it is known that exercises must be performed with specific velocities and motions to be effective, IMUs would be able to collect those data to ensure exercises were performed correctly. Use of IMUs during home exercises would provide objective data regarding how often and how well the exercises were being performed, and this could greatly improve adherence to the treatment plan.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Increased Healthcare Utilization and Costs for Veterans with Blast-Related mTBI

A recent publication from The Long-Term Impact of Military-Relevant Brain Injury Consortium Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) published highlights the increased healthcare utilization and costs for individuals with blast-related (BR) mild TBI (mTBI). Of the 472 Veterans and Service members participating in the CENC longitudinal study, 85 percent experienced mTBI. In the mTBI group, 51.5 percent experienced BR exposures. There was no significant difference between service length and combat deployments with those experiencing mTBI and those with BR mTBI. Individuals with BR exposures presented significantly higher headaches, posttraumatic stress disorder, and anxiety incidences. In addition, individuals with reported BR mTBI had higher levels of diagnosed lower back pain, alcohol and nicotine misuse, and depression.

Increased post-BR mTBI exposure symptoms resulted in increased overall Veteran's Heath Administration (VHA) outpatient healthcare utilization (including primary care, mental health, polytrauma/TBI care, and specialist rehabilitation clinics) compared to non-BR mTBI and those without mTBI. Increased healthcare utilization resulted in a similar trend in VHA outpatient costs: those with BR-mTBI had the highest outpatient costs in 2018, followed by non-BR mTBI and the no TBI group.

In conclusion, individuals experiencing a blast-related mTBI have a higher prevalence of diagnoses of interest, greater utilization of VHA health services, and higher VHA health services costs relative to other groups. It is crucial to monitor these Veterans' long-term outcomes (e.g., employment, quality of life, pain, etc.) to ensure that healthcare systems continue to provide the services they need.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/ Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Integrating New Technologies to Improve Return-To-Duty Decision-Making After mTBI

After mild traumatic brain injury (mTBI), it is vital that military service members are able to proficiently perform dual tasks (e.g. simultaneous motor and cognitive tasks) as well as interact with and function appropriately within their unit when they return to duty. However, there are no standardized, ecologically valid Return to Duty (RTD) assessments for service members that consider these factors. A team at the Cleveland Clinic is filling this gap by developing and validating a series of augmented reality assessment modules utilizing the Rugged Microsoft HoloLens, a single piece of compact, affordable, untethered equipment that can connect multiple users around the world.

These modules allow users to perform tasks that resemble the cognitive and motor demands of military activities with minimal risk to the user and their unit, such as marching while performing a cognitive task, reacting in a simulated combat situation, and performing a small unit operations activity, while also providing objective biomechanical outcomes of performance. Before these biomechanical outcomes from the HoloLens can be applied to more accurately evaluate RTD, it is important to validate them against the gold standard 3D Motion Capture System. In a recent publication, Koop et al. (2020) found that measures of walking such as total distance walked, number of steps, step length, and speed derived from the two systems were statistically equivalent for healthy adults, demonstrating that the HoloLens is appropriate for characterizing walking performance. Next, the researchers will collect normative data on the HoloLens assessments from military personnel including both cadets/officers and enlisted service members. Beyond immediate applications to improving RTD decision making following mTBI, the tools being developed have many potential benefits for service members. In the future, the RTD assessments developed could be used following musculoskeletal injury, behavioral health conditions, or other consequences of blast injury. Additional assessment modules can be developed to evaluate proficiency for specific tasks or civilian occupations, and future applications can be added to guide service-member specific rehabilitation protocols.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Military Operational Medicine Research Program/Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/ Joint Program Committee-8.

Resuscitation with Enteral Fluids: A Prospective Observational Study to Reduce IV-Related Edema Complications

The promise of recent research and development efforts endeavoring to confirm the safety and efficacy of administering non-invasive, oral resuscitation fluid, as an adjunct or replacement therapy to intravenous (invasive) fluid therapy, for life-saving and stabilization of burn injury patients both in the pre-hospital environment and in the hospital setting, is compelling. Burn scientists at the U.S. Army Institute of Surgical Research are conducting a prospective human study to evaluate patients up to one year post-discharge from the hospital regarding the efficacy of enteral (orally-administered) fluid burn resuscitation using oral rehydrating solutions. Human subject enrollment has begun to assess feasibility and safety of the novel, oral fluid resuscitation methodology by evaluating patient outcomes compared to standard of care. Results are anticipated to inform whether implementation of this facile burn fluid resuscitation therapy may enable medical providers of all levels of training to easily, safely, and non-invasively conduct burn fluid resuscitation at all echelons of care for optimal recovery after combat trauma. Outcomes of this work are likely to also yield beneficial impacts for burn and traumatic hemorrhage in the civilian public sector, and for both military and civilian mass casualty events.

Funding support provided by the Combat Casualty Care Research Program.

The Role of Free Fatty Acids in Neuroprotection

Researchers assessed the impact of dietary intake of n-3 polyunsaturated fatty acids (PUFA) following injury (Desai et al., 2021). A diet of reduced PUFA resulted in exacerbation of Morris water maze learning problems, a drastic reduction in N1 amplitude in the visual evoked potential, and greater axonal damage in the optic tract, evident particularly in the injured animals that were deficient in PUFA (Desai et al., 2020).

This work was conducted at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Rockville, Maryland) by funding from the Center for Neuroscience and Regenerative Medicine and the NIAAA Intramural Research Program.

Clinical Trial of 3MDR to Treat PTSD After Mild TBI; With and Without Eye Movement (3MDR) 1

Motion-Assisted, Multi-Modular Memory Desensitization and Reconsolidation (3MDR) is a novel treatment for PTSD, combining aspects of virtual reality exposure therapy (VRET) and Eye Movement Desensitization and Reprocessing (EMDR), within the Computer Assisted Rehabilitation Environment (CAREN). This study aims to obtain an initial estimate of the efficacy of 3MDR in Service members with comorbid PTSD and mTBI, and determine the impact of EM on treatment response. The performance site was located at the Walter Reed National Military Medical Center.

This pilot-prospective, randomized, interventional-controlled clinical trial is designed to obtain an initial estimate of the efficacy of 3MDR in Service members with comorbid PTSD and mTBI and determine the impact of eye movement (EM) on treatment response. Twenty participants are randomized to either EM+ or EM-, receive 10 sessions (three preparatory, six 3MDR treatment, and one conclusion). In preparatory sessions, the therapist and participant select songs and pictures. During treatment sessions, participants walk on the CAREN's embedded treadmill as the 3MDR environment projects on the screen. Sessions begin with a song to bring participants back to the time of their trauma.

Participants walk toward a series of emotionally evocative pictures (four to seven each session) while engaging in a form of "walk and talk" therapy. For each picture, key words are superimposed over the picture and spoken aloud, then for about 30 seconds, participants either follow a red ball across the screen in front of the picture (EM+) or continue walking toward the picture without any ball (EM-). A second song, to bring them back to present day, plays to close each session.

Through November 2021, the target 20 participants have been enrolled, and the final participant is nearing completion of the intervention. Clinically and statistically significant improvement in PTSD symptom severity has been documented with the primary outcome measure, the PTSD Checklist for DSM5 (PCL5).

This study was funded by the Uniformed Services University Center for Rehabilitation Sciences Research, with additional support from the Center for Neuroscience and Regenerative Medicine.

RECONsolidation of Traumatic Memories to ResOLve Posttraumatic Stress Disorder (RECONTROL)

This is a randomized controlled clinical trial to compare Reconsolidation of Traumatic Memories (RTM), an approach with the potential to more rapidly achieve a higher response rate, with the current best-evidenced treatment for PTSD, Prolonged Exposure (PE). The primary intent of this study is to determine whether RTM achieves a greater and/or more rapid response than PE in SMs with PTSD. The performance site was located at the Walter Reed National Military Medical Center. All participants in this study receive active treatment, which the team believes is the only

ethically acceptable approach, though it requires larger numbers to show the benefit of RTM than would comparison to a waitlist or treatment as usual. Eligibility is limited to active or retired Service members who meet criteria for both mTBI and PTSD, including a trauma-relevant flashback or nightmare within the past month. The study targets 108 active-duty Service members or Veterans who are randomized to RTM or PE, for up to ten sessions over two to ten weeks, with at least 24 hours between sessions. The Clinician-Administered PTSD Scale (CAPS-5) is the primary outcome measure, with secondary measures of depression (PHQ-9), anxiety (GAD-7), sleep (PSQI), and functional status (WHOQOL). All are given pre- and post-treatment at two, six, and 12 months. The self-administered PTSD Checklist for DSM5 (PCL5) is completed before sessions two, six, eight, and ten to assess the rapidity of response.

Through November 2021, 47 participants have been enrolled. Those completing the intervention to date have collectively demonstrated a significant improvement in PTSD symptom severity, as measured by the CAPS-5 and PCL5, with a majority no longer meeting the criteria for PTSD.

This study was funded by the Center for Neuroscience and Regenerative Medicine.

Randomized Controlled Clinical Trial of Closed-Loop Allostatic Neurotechnology to Improve Sensory Function and Pain Management after Mild TBI (NEUROTECH)

The purpose of the first randomized, double-blind, two-arm, controlled clinical trial is to evaluate a non-invasive, closed-loop, acoustic stimulation neurotechnology as a novel treatment for symptoms of mTBI, measured by the NSI. The second study seeks to determine whether the duration of the intervention can be cut in half by the addition of electrical stimulation that is also based on one's own brainwaves, at a level that is lower than can be consciously recognized, and of less intensity than the electromagnetic field created by a cellphone, but is delivered at such a precise location that the brain is able to subconsciously identify and respond to it. This effort features two studies. The first is a randomized, single-blind, two-arm, controlled clinical trial, targeting 106 individuals with persisting symptoms after mild TBI (mTBI) who are equally randomized to one of two groups. One group receives ten sessions of closed-loop acoustic stimulation neurotechnology, selected by a computer monitored by a trained technologist, over one to five weeks (Figure 7-18). Each session includes a series of protocols in which sensors are placed on the scalp for monitoring of brain electrical activity. Experimental software algorithms performs real time analysis of brain signals and produce corresponding, representative changing patterns of acoustic stimulation (musical notes of variable pitch and timing), delivered back to the user through standard earbud headphones. The other group receives ten sessions of non-specific acoustic stimulation (musical notes randomly generated by a computer) that mimic the algorithm-guided approach. Both groups undergo the same sequence of procedures and experience comparable levels of social interaction from study investigators and support personnel. The technologist is present with each participant throughout each treatment

FIGURE 7-18: Image provided by USUHS

session. Both participants and those analyzing outcomes are blinded to group allocation. The primary outcome measure is differential change on the Neurobehavioral Symptom Inventory (NSI) scores at three months, and final follow-up is at six months. The second study features a non-inferiority comparison of ten sessions that solely feature musical notes based on the brain's electrical activity versus five sessions of musical notes plus intermittent, very low-level electrical stimulation of the scalp that is also translated from the brain's electrical activity and delivered through the same electrodes that record the brain's electrical activity. This study targets 86 participants, also has the NSI as the primary outcome measure, and follows up with participants for three months after completion of the intervention. The performance sites are located at the Walter Reed National Military Medical Center and the Womack Army Medical Center.

Through November 2021, the target enrollment has been achieved, and the intervention completed, for 106 participants in the first study, with the final participants completing their six month follow-up before the end of the 2021 calendar year. While the researchers remain blinded until complete, all participants—including those receiving the sham intervention—evidence statistically and clinically significant improvements in the NSI score. In addition, 11 participants have been enrolled in the second study, and completion is anticipated by September 2022.

This effort was managed by CDMRP with support from the Psychological Health and Traumatic Brain Injury Research Program and Military Operational Medicine Research Program/ Joint Program Committee-5 and Clinical and Rehabilitative Medicine Research Program/Joint Program Committee-8.

Consortium Studies

Intermediate-Term Effects of Concussion and/or Repetitive Head Impact Exposure

The Concussion Assessment Research and Education (CARE) Consortium, established in 2014, is the largest multi-site study of the natural history of concussion in both sexes, multiple sports, and military service academy cadets. It continues to be prolific in the dissemination of findings regarding the intermediate-term effects of concussion and/or repetitive head impact exposure in military service academy cadets and National Collegiate Athletic Association (NCAA) student-athletes. Findings from the CARE Consortium for the FY21 performance period may inform several aspects of TBI etiology (including possible risk factors and concussion mechanisms), clinical assessment (including clinical profiles), and recovery (including sex differences).

Regarding etiology, CARE findings suggest that altitude and heat index at the time of injury do not contribute to clinically meaningful changes on acute assessments or concussion recovery. Additionally, a predictive model was developed, using only baseline data, that identified athletes and cadets who would go on to sustain sport-related concussions. This model had comparable accuracy, for identifying concussion, to many existing concussion assessment tools, which may provide further insight into potential concussion risk and protective factors.

Regarding clinical assessment, it was found that several individual assessments lack both sensitivity and specificity for diagnosis and, furthermore, ICD-10 symptom criteria can be mimicked by pre-existing conditions, insufficient sleep, and/or stress. These findings support the necessity of person-specific, multi-dimensional assessment for concussion diagnosis, which may include symptom evaluation, postural control assessment, neuropsychological status, blood

Photo credit: Seaman Luke Cunningham/ U.S. Navy

biomarkers, and other functional assessments, such as those of the vestibular and oculomotor systems (using the VOMS tool) and normative-based cutoff scores for reaction time tests.

Regarding sex differences in recovery, CARE findings showed no difference in recovery between sexes across comparable collegiate sports; however, disparate outcomes were found in the recovery times, which may indicate that, while intrinsic biological sex differences in concussion recovery may exist, important, modifiable extrinsic factors may play a role in concussion outcomes. This research was published in *Br J Sports Med.* (Master et al., 2020); *Sports Med.* (Castellanos et al., 2020); *Sports Med.* (Lempke et al., 2021); *Am J Sports Med.* (Ferris et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Evidence-Based Methodology for Evaluation of Clinical Outcome Assessment Measures for TBI

Treatment and diagnostics for TBI have been the subject of research, development, and clinical trials for over two decades. This topic receives significant media attention with respect to Service members, Veterans, and professional sports athletes. Until early 2018, there were no FDA-approved diagnostics or therapies specific for TBI. Well-defined endpoints and changes to the clinical trial design are needed in order to support successful regulatory-driven development of diagnostics and therapeutics for TBI. This includes advancing the identification, validation, implementation, and dissemination of clinical outcome assessments (COAs) and biomarkers for acceptable in regulatory

review of FDA-qualified medical device and drug development tools for mild to moderate TBI. The TBI Endpoints Development (TED) Initiative, led by the University of California, San Francisco, seeks to provide the foundational framework for improved clinical trials which can be used to support regulatory approvals for TBI diagnostics and therapeutics. The TED Initiative represents a network of public and private partnerships in a team science approach to collectively advance the field of regulatory science for TBI.

In FY21, researchers from the TED Initiative reported the development and pilot-testing of an Evidence-Based Clinical Outcome Assessment Platform (EB-COP) that can be used to systematically evaluate suitability of TBI-specific COAs with respect to specific use cases. The EB-COP platform follows previous efforts by the TED initiative to review the existing literature and published guidelines on psychometric standards for COAs. The team used this information to develop a six-step, semi-automated platform to grade COA performance on the following: diagnosis, symptom detection, prognosis, natural history, subgroup stratification, and treatment effectiveness. The EB-COP framework was evaluated using a modified Delphi consensus-building process and subsequently incorporated into a specific software platform. Pilot testing was performed using the Glasgow Outcome Scale-Extended and shown to be a feasible method of COA selection early studies. Additional testing and validation of the EB-COP against other COAs will be necessary (Christofouru et al., 2020).

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

New Descriptors of Symptoms Following mTBI

Utilizing the rich resource that is the longitudinal study supported by the Chronic Effects of Neurotrauma Consortium (CENC) and Long-Term Impact of Military Brain Injury Consortium–Chronic Effects of Neurotrauma Consortium (LIMBIC–CENC), new insights have been found on mild TBI (mTBI) and sleep, posttraumatic stress disorder (PTSD) and other symptom burden, and brain density. These new findings help to expand the knowledge of how best to care for and support Service members and Veterans post-mTBI.

Veterans and Service members with a history of mTBI were more likely to be categorized as high-risk for obstructive sleep apnea (OSA). This increased OSA risk was significantly associated with worse cognitive (thinking and memory) performance and greater symptom burden (Garcia et al., 2020). As OSA is a treatable condition, there may be ways to relieve and prevent OSA-related cognitive loss and provide quality of life gains to individuals living with TBI.

Additional analyses show that individuals with TBI, particularly those with polytrauma, had increased severe symptom reporting compared to moderately healthy counterparts, irrespective of sociodemographic factors (Bouldin et al., 2021). One such increased comorbidity is PTSD: in one group of participants from the longitudinal cohort, 40.5 percent of individuals with mTBI screened positive for PTSD. Fewer than 24 percent of participants without a history of mTBI screened positive for PTSD. Participants with a history of mTBI reported higher elevations of neurosensory and posttraumatic stress symptoms compared with those without a history of mTBI (O'Neil et al., 2021).

Further insights linking the physiological reasons for these elevated and persistent symptoms are under investigation. A concern among aging individuals with TBI is the risk for neurodegenerative disorders, including Alzheimer's

Photo credit: Tech. Sgt. Anthony Wood/ U.S. Air Force

disease and other dementias. A neuroimaging study on the CENC cohort has revealed that, in individuals with multiple or repetitive mTBI, increasing age was associated with lower cortical blood flow in areas of the brain typically affected by Alzheimer's disease. Interestingly, mTBI did not moderate associations between age and cortical thickness (p's>05), suggesting that decrease in brain density was not moderated by mTBI. Much more is to be done to investigate how decreased cerebral blood flow is linked to post-TBI symptoms.

Overall, many explorations and analyses are underway utilizing the LIMBIC–CENC cohort and databases. These represent a rich resource to learn more about how Service members and Veterans experience and live with TBI, as well as physiological insight into how symptoms and comorbidities develop.

This effort was managed by the Congressionally Directed Medical Research Programs with support from the Psychological Health/Traumatic Brain Injury Research Program and with programmatic oversight by the Combat Casualty Care Research Program/Joint Program Committee-6.

Center for Rehabilitation Sciences Research

The Center for Rehabilitation Sciences Research (CRSR) at the Uniformed Services University of Health Sciences (USUHS) was established to lead rehabilitation-related research within the Military Health System to optimize the rehabilitative care for Service members with combat-related injuries to promote their highest functional recovery, independence, and quality of life. Given the high prevalence of blast-related trauma causing amputation, TBI, and PTSD, many of the CRSR activities are directly related to blast research. In 2021, those research efforts included the Photomedicine to Enhance Military Readiness program — a four-year collaboration with the Wellman Institute, DJO, Geneva Foundation,

The Henry M. Jackson Foundation (HJF), and Spaulding Rehabilitation. These teams are executing nine clinical and translational research projects to assist with nerve graft healing and deliver optimal dosimetry of photobiological therapy to enhance performance and reduce the potential for musculoskeletal injury. The team will continue to work on peripheral nerve repair and vascularization using 3D-printed collagen as a natural biomaterial, improving recovery times after exertion, and augmenting wound healing with antimicrobial dressings. The Regenerative Rehabilitation Laboratory has finalized and submitted modifications to the Institutional Animal Care and Use Committee protocol. This protocol is expected to receive approval by end of this year in order to complete in vivo experimentation evaluating photobiomodulation treatment, along with 3D-printed collagen nerve grafts in peripheral nerve repair. The team had three abstracts accepted to the 2021 Military Health System Research Symposium as well as one abstract accepted to Association of Military Surgeons of the United States for a poster presentation in February 2022.

In addition to these clinical and translational research projects, CRSR continues to provide leadership and coordination of the Military Treatment Facility Engagement Committee (MTFEC) within the Pain Management Collaboratory (PMC) Coordinating Center (PMC3), which is an interagency initiative to support a multi-component research effort focused on non-pharmacological approaches for pain management. Four ongoing pragmatic trials studying non-pharmacological approaches to pain for Service members and Veterans continue. Collaboration continues between the U.S. Department of Veterans Affairs, DOD, and the Defense Health Agency (DHA) to improve policies and procedures to enhance clinical research execution within the DOD.

From the Center's Core Portfolio, a major ongoing research effort since 2019 is the "Big Dog Study," formally titled "Biopsychosocial Effects of Service Dog Training Program (SDTP) on Posttraumatic Stress (PTS) and Post-Concussive Symptoms (PCS)." In addition to evaluating the biopsychosocial efficacy of SDTP as an adjunct therapy of the current standard of care for individuals with PTS and PCS, this multi-disciplinary, collaborative project within the National Capital Region also aims to evaluate participants' overall experience with and perceptions of SDTP using qualitative interviewing. To date, the CRSR research teams at Fort Belvoir and Walter Reed National Military Medical Center have enrolled 125 out of the target 156 participants, who have completed or have ongoing SDTP sessions with trainers provided by our sub-awardee, the Warrior Canine Connection (WCC). Additionally, the team has developed four abstracts which have been presented at national conferences. Two abstracts have been presented that pertain to the Service Dog Training Program and its impact on mental health care utilization. Manuscript development is anticipated in 2022 once recruitment and data analyses are complete.

Another of CRSR's groundbreaking investigations through the Center's Core portfolio includes "A Retrospective Study of Healthcare Utilization of Patients with Limb Loss and Severe Limb Trauma within the Military Health System." This is one of the first studies proposed to estimate health care cost and service utilization patterns of patients with severe limb trauma and limb loss who were rehabilitated at military treatment facilities in the United States. This study aims to provide a comprehensive analysis of how amputation or limb salvage, and the associated treatment, impact individuals and their family unit. While analysis is ongoing, a manuscript titled "COVID-19: A Catalyst for Change in Virtual Healthcare Utilization for Persons with Limb Loss, A Literature Review," was published on April 18, 2021.

Photo credit: 1st Lt. Ryan DeBooy/ U.S. Army

Additional funding has been secured by the NCAA/DOD Concussion Assessment, Research, and Education (CARE) Consortium for the CARE/ SALTOS Integrated (CSI) study. CSI will include the recruitment of 2,000 participants at the Naval School Explosive Ordinance Disposal (EOD) at Eglin Air Force Base. The study will establish a neurobiopsychosocial baseline during the EOD program, and participants will become eligible for longitudinal follow-up via electronic survey after one year.

Conclusion

It is an honor for BIRCO to share so many accomplishments from across the blast injury research and development community in FY21. The breadth of research topics and outcomes 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, and 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. BIRCO 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.

08

Photo credit: Edwin Wriston/U.S. Army

CHAPTER 8:

WAY FORWARD

The DOD Blast Injury Research Coordinating Office (BIRCO) continues to facilitate collaboration and the sharing of knowledge among blast injury researchers. Going forward, there are several existing and planned efforts that will achieve the DOD Directive to maintain a DOD technology base for medical research related to blast injuries; perform programming and budgeting actions for all blast injury research based on analysis and prioritization of DOD component needs; provide medical recommendations on MHS blast injury prevention, mitigation, and treatment standards; and ensure that blast injury research information is shared. This chapter highlights the continued efforts of BIRCO to address the DOD Directive.

BIRCO Initiatives and Engagements

Ongoing and future BIRCO initiatives and engagements aim to provide critical information on capability gaps identified by Congress, DOD working groups, and through the vast collaborations with scientists, clinicians, and engineers from across the blast injury research community and initiatives like the International State-of-the-Science Meeting series. These efforts ultimately seek to address the overall knowledge gap in the understanding of blast-related injuries to improve Service member quality of life and return to duty.

Blast Injury Prevention Standards Recommendation Process

BIRCO will continue the Military Health System (MHS) Blast Injury Prevention Standards Recommendation (BIPSR) Process for Auditory and Dermal Burns Blast Injury Types. The MHS BIPSR Process is 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 personal protective equipment development and performance testing.

Reprioritization of BIPSR Process Blast Injury Types

To ensure the current needs of the operational environment and the DOD are met, BIRCO plans to perform a reprioritization effort for the remaining seven MHS BIPSR Process Blast Injury Types not completed or underway in FY21-22: Ocular, Face, Neck, Thorax, Abdomen, mild traumatic brain injury (mTBI), and Moderate/Severe TBI. The reprioritization effort will again apply an established mathematical analysis technique, multi-attribute utility theory (MAUT), a widely used and accepted methodology for guiding tradeoffs among multiple objectives. The Evaluation Factors and scoring scales used in the MAUT methodology provide a framework for capturing subjective assessments to support an objective and unbiased decision-making process. BIPSR Process Stakeholders will provide inputs to the reprioritization process to ensure that the outcomes reflect current DOD priorities.

Auditory Blast Injury Type

A series of meetings are planned to include the Subject Matter Expert (SME) Panel discussion of detailed findings from the Candidate Standards evaluation process and the development of a draft auditory blast injury prevention standard recommendation for consideration by the BIPSR Process Stakeholders. As the next step, a Consensus-Building meeting is planned for FY22 involving Stakeholders, Candidate Standard developers, academia, industry, and government SMEs to share findings and allow for discussion and final development of the auditory blast injury prevention standard recommendations and identify remaining knowledge gaps for dissemination to the research community.

Additionally, in FY22, BIRCO plans to finalize and release the previously described Automatic Waveform Anomaly Real-Time Detector (AWARD) tool for use by the community. This prototype software supports the detection of common data anomalies (i.e., microphone clipping, low signal-to-noise ratio, DC shift) to inform the appropriate use

ⓘ Acronyms and references used in this chapter are included in Appendices A and B.

Photo credit: Tech. Sgt. Emily Moon/U.S. Air Force

of data, including the potential need for additional data collection. The approach was developed in MATLAB for the easiest transition to research and data acquisition communities following documentation and finalization of the tool.

MHS Blast Injury Prevention Standards Recommendations (BIPSR) Process for the Dermal Burns Blast Injury Type:

In FY22, BIRCO will initiate planning efforts for the Blast Injury Prevention Standards Recommendations (BIPSR) Process Dermal Burns Focused Stakeholder Committee, expected to convene in FY23. Initial activities include completing the existing capabilities review. This review includes an initial literature survey to identify potential candidate standards and yield an initial list of Subject Matter Experts (SMEs) with relevant domain expertise. SMEs will be interviewed to discuss identified candidate standards capabilities and additional pertinent information. Other planned activities include drafting a request for information to obtain additional existing dermal burn blast injury criteria, thresholds, standards, and models; identifying gaps between existing knowledge and knowledge needed to inform standards; engaging PPE developers on standards identification, development, and research; identifying additional relevant researchers; identify science and technology resources for continuous platform improvements, and obtain further information from industry, academia, and federal agencies. BIRCO will engage with stakeholders from across the DOD and communities of interest to ensure representation in the Dermal Burns Focused Stakeholder Committee. At the kickoff meeting planned for FY23, the Focused Stakeholder Committee will be briefed on an overview of the BIPSR process, learn about candidate standards, findings to date, and establish the next steps.

Blast Overpressure Studies Working Group

BIRCO supports the FY18 National Defense Authorization Act (NDAA), Public Law 115-91, Section 734 program, Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats, and international collaborative activities as the Office of Primary Responsibility for Line of Inquiry (LOI) 2 Weapons Systems. BIRCO will continue to collect, collate, summarize, and analyze information and findings to develop strategies and recommendations, and inform policy and guidance for improved warfighter range safety. BIRCO will establish the LOI 2 Blast Overpressure (BOP) Tool Module Sub-Working Group to inform refinement, validation, testing, and integration of the BOP Tool module and convene to inform and identify requirements. An independent assessment team will be established to support the BIRCO LOI 2 BOP Tool Module efforts. LOI 2 will initiate the development of a draft technical report which will capture the approach, findings, and recommendations.

Computational Modeling Working Group

The DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats (DOD Working Group) aims to shape, focus, and coordinate efforts to enable a capability for the computational modeling and simulation (M&S) of human lethality, injury, and impairment resulting from the entire spectrum of blast-related threats and environments, from the initial point of interaction with the blast hazard to return-to-routine. In FY22, the DOD Working Group plans to finalize a strategic plan with actionable, impactful guidance and recommendations for establishing a DOD Computational Human Body Modeling Capability that can provide decision-makers with credible, impactful simulation-based results, as well as the development of the Computational Human Body Modeling Framework to support model selection for in silico scenario development, scenario execution, analysis of results, and more.

Working group activities will address identifying, communicating, and coordinating focus areas to accelerate the advancement of M&S for the Modeling Capability and to align efforts within the DOD Digital Engineering strategy, continued development of Modeling and Data Sources Registries, and identifying potential steward organizations for the registries in perpetuity. The working group will also foster engagement with and commitment to the Framework and Modeling Capability through established and new pathways. These activities will entail continued engagement with the National Academies to further mutual goals and promote coordination among the many M&S efforts to improve protection and survivability from blast injury.

International Forum on Blast Injury Countermeasures

In FY22, BIRCO plans to host the 6th International Forum on Blast Injury Countermeasures (IFBIC) in McLean, VA. The objectives for the 6th Forum are to assemble an international forum focused on multidisciplinary science and medicine necessary to increase our understanding of blast injury and its countermeasures from bench to bedside, achieve a mutual understanding of international efforts in blast injury research, identify knowledge gaps requiring collaborative research, and increase understanding and promoting further collaboration to improve prevention, clinical diagnosis, and treatment addressing the entire spectrum of blast-related injuries. It is expected that meeting participants to hear about research and findings related to blast injury epidemiology and environmental sensing of blast shockwave hazards; primary blast injury (due directly to shockwave effects); secondary (penetrating ballistic fragments) and tertiary (acceleration and blunt force) blast injury

long-term effects; cumulative effects, and chronic symptoms due to blast exposure; prevention, mitigation, and treatment of blast injuries; diagnostic measures/biomarkers, computational modeling, and simulation of blast phenomena and blast injury; characteristics comparisons between blast-related TBI and blunt TBI and new technology and methods for blast injury research and medicine.

Contributions from all countries, seasoned researchers, and young investigators are welcome to submit their work efforts for presentation. These meetings have been very productive, involving active and fruitful discussions and exchange of creative ideas on a broad spectrum of blast injuries; identifying critical issues involving experimental and computational studies of blast-induced injuries; and creating new partnerships on joint research explorations to address the many scientific and technical challenges facing the field.

International State-of-the-Science Meeting Expert Panel Recommendations

Expert Panel recommendations from the annual International State-of-the-Science Meeting (SOS) provide important insights into current capability gaps and requirements. The SoS meeting series leverages the expertise of outstanding scientists, engineers, and clinicians to identify knowledge gaps and to inform future research needed to close the gaps in the prevention, mitigation, and treatment of blast injury (read more in Chapter 2).

The SoS meeting scheduled for FY21 was canceled due to the COVID-19 pandemic. In FY22, domestic and international stakeholders from across the DOD, other federal laboratories, academia, and industry will convene at the tenth SoS meeting, "Understanding the Computational Modeling of the Human Body's Responses to Blast-Related Injury."

NATO Human Factors and Medicine Panel Research Technical Groups

Building upon previous successes, the NATO Human Factors and Medicine (HFM) Panel established the NATO HFM-341 Research Technical Group (RTG) for the "Validation of Modeling and Simulation Methodologies for Human Lethality, Injury, and Impairment from Blast-Related Threats. The objective of this RTG is to develop standardized methodologies and criteria to validate computational models and simulation approaches for the entire spectrum of blast-related injuries to mounted and dismounted military personnel. In FY22, the NATO HFM-341 (RTG) plans to organize a Kickoff Meeting in Paris, France, in June 2022. During the kickoff meeting, technical team members will review the Technical Activity Proposal and develop a Program of Work.

In addition, BIRCO will co-chair the newly formed NATO HFM-Exploratory Team-192 with the U.S. Army Military Operational Medicine Research Program (MOMRP). The primary purpose of this exploratory team-Blast Exposure Monitoring in Military Training and Operations-is to understand Service members' occupational health hazards resulting from repetitive use of weapon systems and explosives during their military career.

JTAPIC Initiatives and Engagements

The ongoing and future JTAPIC initiatives and engagements streamline and support information sharing and collaboration on incident analyses on theater combat-related events by leveraging JTAPIC partnerships within the DOD, across other governmental agencies, and with international allies. JTAPIC aims to provide actionable analysis of medical, intelligence, operational, and material information (the cause and effects) to improve the understanding of vulnerabilities to threats and to enable the development of improved tactics, techniques, and procedures (TTP) and material solutions that will prevent or mitigate traumatic injuries. Each event's multi-disciplined and

Photo credit: Lance Cpl. Madison Santamaria/U.S. Navy

multi-community analyses provide actionable decision support to inform solutions across the doctrine, organization, training, materiel, leadership, education, personnel, facilities, and policy domains that will prevent or mitigate traumatic injuries during all military operations and, ultimately, in combat.

Key JTAPIC Initiatives in FY22

- Reestablish communications and collaborations with key stakeholders, current and future partners; and the Office of the Joint Staff to improve reporting and survivability efforts
- Redefine incident monitoring and development of Current Operations Incident Report (COIR) to enhance support to all Combatant Commands
- Track, maintain, and provide rapid response to requests for information to ensure actionable information is shared as broadly as possible and in accordance with DOD standards
- When there is evidence for possible trends in event data, collaborate with JTAPIC Partners to produce push products and disseminate them to the relevant communities of interest
- Continue to deliver the Annual Casualty and Operations Rollup report to provide military practitioners with context for casualty-producing events and associated medical outcomes
- Further develop and provide a unified, secure information management system, the JTAPIC Information and Collaboration System (JINCS), which serves as a collaborative environment for the collection, integration, analysis, and storage of both classified and unclassified information

Current Operations Incident Report (COIR)

JTAPIC will continue to monitor and develop COIRs (detailed operational and injury reports) as casualty-causing combat incidents occur. Through the coordinated effort of JTAPIC PMO, the JTAPIC Internal Program Management Support (JIPMS) team, and other JTAPIC Partners, expert incident analysis and reporting, JTAPIC provides insight to support unit-level TTPs, course-of-action development, training scenario development, and drive requirements. In FY22, JTAPIC will focus on the development of COIR to improve combat vehicle platforms for U.S. Central Command and U.S. Indo-Pacific Command and training activities.

Proposed COIR Topic(s):

- JTAPIC will provide analyses of U.S. Central Command combat incident analyses to inform combat vehicle materiel developers' recommendations to improve vehicle and personnel survivability
- JTAPIC will team with DOD and non-DOD logistics organizations to improve rear and forward support to the operational Combatant Commands
- Coordinate with International Allies to develop and update NATO standardization agreements (STANAGs) to improve vehicle and personnel survivability
- Improved collaboration with operational, logistics, and international allies will improve combat vehicle and warfighter survivability in the future fights

Requests for Information

JTAPIC will continue to expand and leverage cross-agency partnerships to respond to and develop actionable analysis products for customer requests to aid in completing combat or accident event analysis. In FY22, JTAPIC will continue to build upon the momentum from FY21 and provide analyses for the eleven active, five closed, and fifteen completed requests. Responding to these requests for information will provide valuable information to the requesting organizations and, where applicable, to communities that would benefit from these knowledge products.

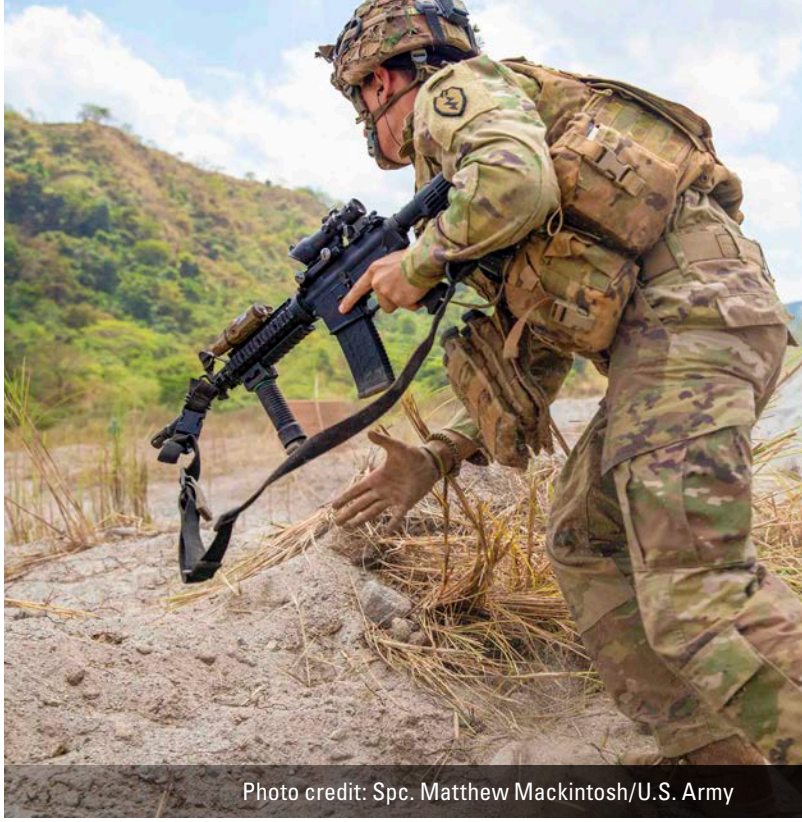


Photo credit: Spc. Matthew Mackintosh/U.S. Army

Focus Areas in FY22

- JTAPIC will collaborate with DOD and non-DOD Research and Development (R&D) organizations to shape research projects to improve vehicle and personnel survivability
- JTAPIC will improve reporting of Potentially Concussive Events to the Office of the Joint Staff Surgeon and Defense Health Agency in support of the DoDI 6490.11, DOD Policy Guidance for Management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting
- JTAPIC will establish relationships with other governmental agencies to further contribute to the Whole-of-Government Approach to Force Protection efforts
- Improved collaboration with R&D, the Office of the Joint Staff Surgeon, and other governmental organizations will help maximize resources to improve combat vehicle and warfighter survivability in future fights

Photo credit: Lance Cpl. Andrew R. Bray/U.S. Army

Push Products

JTAPIC will continue to monitor, track, and provide analysis for casualty-causing incidents throughout the Combatant Commands through the JTAPIC Information and Collaboration System and the JTAPIC Concussive Event Reporting System, as well as systems owned and operated by JTAPIC Partners. If trends require further internal investigation, JTAPIC will deliver push products that address these areas of interest.

Annual Casualty and Operations Rollup

The Annual Casualty and Operations Rollup is an annual analytical operation and casualty report that provides military practitioners context for casualty-producing events and associated medical outcomes. The published report will be released around the second quarter of the calendar year 2022 to the JINCS Product Library (https://jincs.army.mil/Index?returnUrl=/HomePage) and Lessons Learned Community on milSuite (https://www.milsuite.mil/book/groups/call).

JTAPIC Information and Collaboration System (JINCS)

The purpose of the JINCS is to provide a unified, secure information management system that serves as a collaborative environment for the collection, integration, analysis, and storage of both classified and unclassified information. The JTAPIC Concussive Event Reporting System (JCERS) will fully integrate with the JINCs in FY22, allowing users to report potentially concussive events by submitting an online form or uploading batch information in the case of mass-casualty events. The integration of these systems provides easy access to users, facilitating reporting from the Combatant Command level (or its designee) to JTAPIC in accordance with DoDI 6490.11.

NASEM Recommendations for TBI

In FY21, the DOD commissioned the National Academies of Sciences, Engineering, and Medicine (NASEM) to assemble a committee of TBI experts to gather input from the public and private experts and stakeholders; explore and assess the public and military health burden of TBI; examine the current landscape of TBI research; and consider such issues as improving TBI systems of clinical care from acute care through rehabilitation. In FY22, we await the NASEM recommendations from this study, which includes the *Accelerating Progress in Traumatic Brain Injury (TBI) Research and Care* workshops held in March/April 2021. The NASEM committee charged with making the recommendations will be assessing:

- Major barriers and knowledge gaps that are impeding progress in the field
- Opportunities for collaborative action (both intergovernmental and public-private) that could accelerate progress in TBI research and care
- A roadmap for advancing both research and clinical care that would guide the field over the next decade

Ongoing and Future Blast Injury Research and Development Efforts

The prevention, mitigation, and treatment of blast injuries cannot be addressed without the cooperative efforts of organizations across the DOD, other federal agencies, academia, industry, and international partners. The blast injury research and development community submitted the following efforts as example initiatives that will continue to address blast injury challenges in FY22 and beyond.

Supporting Clinical Research

Facilitating More Efficient Research Participant Recruitment

Study recruitment is a challenge across TBI and posttraumatic stress research. To address this, the Center for Neuroscience and Regenerative Medicine (CNRM) at the Uniformed Services University of the Health Sciences (USU) developed the TBI Research Opportunities and Outreach for Participation in Studies (TROOPS) referral program. TROOPS addresses the difficulty of recruiting participants for research studies, with a particular focus on TBI and posttraumatic stress. TROOPS is a web-based referral program that expedites and enhances the participant recruitment and referral process. Prospective study participants can directly self-enroll via a web-based platform accessible from a computer, tablet, or smartphone. Referral program staff pre-screen enrollees for eligibility in participating studies and provide contacts to study teams. This process eases the burden of recruitment for study teams by providing a registry of willing study participants with a variety of relevant medical histories and military backgrounds.

Studies interested in using the TROOPS referral program can send an active study protocol and consent form to **CNRMstudies@usuhs.edu.** Study teams are required to complete an impact statement to be approved by CNRM leadership and provide a statement regarding TROOPS in the recruitment section of their protocol. There is no cost associated with utilizing TROOPS referrals. Participating studies are largely focused on military cohorts, but the TROOPS referral program is not limited to military-based studies. TROOPS enrolls active-duty Service members, Veterans, and civilians. In 2021, TROOPS provided 4 percent of target study enrollment across all participating studies, and 56 percent of referrals were successfully enrolled.

Leveraging Expertise in Biomarkers and Informatics to Support Clinical Research

USU CNRM Clinical Research supports state-of-the-art, CNRM-funded, collaborative research initiatives through the Biomarkers Core. The Biomarkers Core collaborates with the Biospecimen Repository to process, catalog, analyze, and store biosamples (primarily blood) from research that studies military personnel and civilians with TBI. In addition to processing and storing study biosamples, the Biomarkers Core provides advanced analysis methods to evaluate epigenetic modifications; mRNA, circular and noncoding RNA expression; and high sensitivity protein assays for various proteins-including tau, neurofilament light, and glial fibrillary acidic protein. In early 2022, the Biorepository will add onsite analytic capabilities, which include the installation and maintenance of a Single Molecule Array (Simoa, Quanterix), allowing collaborators to use this analysis method for high sensitivity of brain injury related proteins. More information about the Biomarkers Core is available at **cnrm-biospecimen-repository-ggg@usuhs.edu.**

The Informatics Core offers a variety of resources and data support services to accommodate all stages of a study's life cycle and a broad range of data types for clinical trials, translational research, operational research initiatives, and collaborative studies. The Informatics Core ensures each study participates in the TBI research community's data standardization efforts and requires projects to incorporate the National Institute of Neurological Disorders and Stroke's TBI common data elements, unique data elements, and form structure. These resources and services the Informatics Core manages are for various platforms, such as CNRM's Collection, Access, Sharing, and Analytics Platform (CASA), Data Repository, Electronic Case Report Form Library, and TBI Research Opportunities and Outreach for Participation in Research Studies (TROOPS).

The Informatics Core's range of support services is not limited to offering studies assistance with data collection and management, software development and testing, quality assurance, statistical development and analysis (e.g., data modeling and machine learning), and informatics consultation (e.g., identification of a project's resources and needs). It also facilitates the submission of de-identified data to CNRM's Data Repository and the FITBIR informatics system. More information about the Informatics Core is available at **CNRMInformatics@usuhs.edu.**

DOD/USU Brain Tissue Repository

The DOD/USU Brain Tissue Repository (BTR) was developed under the auspices of the Center for Neuroscience and Regenerative Medicine (CNRM) of the Uniformed Services University of the Health Sciences (USU) and has now evolved into a separate facility that supports research on military TBI. Housed on the USU campus, the BTR is a brain bank dedicated to collecting brain specimens from deceased Service members, both active duty and retired, following consent for donation and use in research from their legally authorized representative. This facility is the only brain repository exclusively dedicated to exploring the effects of a military career (including blast exposure) on the human brain.

At the end of 2021, the DOD/USU BTR had 269 brain specimens, all derived from military personnel. The specimen collection includes a significant number of individuals who had served in the War Against Terror over the past 20 years and were heavily exposed to blasts in training and during deployments. In addition, brain specimens from Service members who were not deployed and served without blast exposure are in the collection and can serve as controls for comparison. The legally authorized representative for each Service member's donated brain provided consent for its use in research. Each donated brain is subjected to detailed neuropathologic characterization, dissected, and stored to maximize its usefulness in modern neurobiological research.

A total of 27 research laboratories, including government-affiliated, academic, and other research institutes, have received brain samples from the DOD/USU BTR to support research on blast exposure and other military-relevant subjects. Over 40 peer-reviewed publications have emerged from the DOD/USU BTR and from research conducted on specimens distributed to other research laboratories, most dealing with blast-related topics. Analysis of these specimens has resulted in characterizing aspects of the "invisible wound." The work on developing new diagnostic neuroimaging approaches to blast-exposed Service members described on page 151 of this report was carried out in collaboration with the DOD/USU BTR and utilized its tissue bank resources and neuropathology expertise. In addition, the work on chronic blast effects in the ferret described on page 143 provides evidence that this animal model shows promise in replicating actual damage to brain tissue seen in blast-exposed Service members.

The DOD/USU BTR provides information on the morphologic, biochemical, and molecular effects of blast exposure on the human brain and on alterations that occur under conditions of military service. Attempts to model these effects using animal experimentation must eventually turn to the work of the DOD/USU BTR for validation. This facility is uniquely positioned to identify knowledge gaps and provide solutions that illustrate the nature of blast and its effects on the human brain. The work of the DOD/USU BTR continues, with increasing numbers of brain specimens donated each week by military families supporting the BTR's effort.

The DOD/USU BTR receives ongoing funding support from the Defense Health Agency.

Injury Prevention

Research and development efforts in this category aim to prevent blast injury across the spectrum of potential injuries by establishing safety thresholds for human exposure to blasts, supporting the design of protection systems, and strengthening guidelines for the safe use of weapon systems. An example from DOD's many new and continuing injury prevention research projects follows.

INVestigating traIning assoCiated blasT pAthology (INVICTA)

The INVICTA study, led by CNRM with collaboration from WRAIR, is a five-year effort to address concerns about the acute, cumulative, and long-term impact of repeated subconcussive blast exposure on the brain from high explosives and heavy weapons training. INVICTA is a prospective observational study featuring a detailed baseline assessment of U.S. Navy SEALs and Range Safety Officers, with serial assessments through three months for SEALs and two years for Range Safety Officers. Assessments include a wide range of blood biomarkers, cognitive testing, and a series of novel measures of sensory, motor, and physiologic performance. A better understanding of repeated subconcussive blast exposure and its acute, sub-acute, and chronic impacts on brain health will inform guidelines to promote enhanced safety in training. This study, sponsored by the Defense Health Agency, is part of the work addressing FY18 NDAA, Public Law 115-91, Sec. 734 and subsequent related legislation.

Acute Treatment

Studies in this category seek to develop new diagnostic tools, clinical guidelines, therapies, and medical interventions to treat the spectrum of blast-related injuries to improve survivability and mitigate long-term disability for Service members with blast-related injuries. Two examples from DOD's many new and continuing acute treatment research projects follow.

Measuring the Effects of Erenumab Antibodies to Treat Acute Posttraumatic Headache in Military Service Members and Civilians with Mild Traumatic Brain Injury

Researchers at the USU are researching the effectiveness of erenumab for the treatment of posttraumatic headache. The purpose of this study is to determine if erenumab, a monoclonal antibody (mAb) that is specific to the CGRP receptor, is safe, effective, and suitable to treat PTH following an mTBI. Secondary objectives are to evaluate the safety and patient tolerance of erenumab, and the impact of the antibody against the placebo across several variables, including monthly headache days, time to return to duty, work activity, headache disability, depressive symptoms, and insomnia.

The canonical calcitonin gene-related peptide (CGRP) research project is a randomized, double-blind, placebo-controlled study assessing the safety, drug tolerability, and efficacy of erenumab 140 mg (Aimovig®) for the treatment of acute posttraumatic headache (PTH) in approximately 360-404 military Service members and civilians with mild traumatic brain injury (mTBI). The primary objective is to measure the effectiveness of erenumab over the monthly headache days during the double-blind treatment phase (Week 8 to Week 12). The treatment phase occurs during the first three visits (up to Week 12), followed by a four-week safety extension. The study will be performed at three to five selected military treatment facilities over a five-year period, enrolling male and female military Service members and civilians between the ages of 18 and 50.

Using Repetitive Transcranial Magnetic Stimulation Protocols for the Treatment of Depressive Symptoms

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation technique that modulates cortical activity and network connectivity. The technique is FDA-cleared for treatment-resistant major depressive disorder. Researchers at Walter Reed National Military Medical Center, Fort Belvoir Community Hospital, Brooke Army Medical Center, William Beaumont Army Medical Center, Naval Hospital Camp Pendleton, and Naval Medical Center San Diego sought to determine the efficacy, safety, and tolerability of a variety of rTMS protocols for the treatment of depressive symptoms in a large sample of current and former U.S. military Service members with a history of concussion.

The study sample will include up to 440 Service members who will receive 20 rTMS sessions over a five-week period. The Bayesian adaptive design will evaluate the targeting strategy, laterality of stimulation, and protocol parameters to determine an optimal rTMS protocol for the treatment of depression. The primary efficacy outcome will be a change in depressive symptom severity from Baseline to Post-rTMS, based on the interview-based Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcome measures will include self-reported depressive symptoms, assessments of the quality of life, PTSD severity, cognitive function, and rsfMRI connectivity changes relevant to mood regulation from Baseline to Post-rTMS. Exploratory analyses will include durability of effects during the six months following the Post-rTMS Evaluation.

Photo credit: Senior Airman Zachary Rufus/U.S. Air Force

Reset

This research category describes investigations that extend beyond rehabilitation to include all activities necessary to return injured Service members to duty or productive civilian life. Reset includes research to advance strategies for reducing recovery time, improving rehabilitation programs, maximizing opportunities for return-to-duty and reintegration into the civilian workforce, and improving the quality of life for Service members who have experienced blast-related injuries. Four examples from DOD's many new and continuing reset research projects follow.

CAREN versus Augmented Reality: Expanding 3MDR Therapy for PTSD: A Randomized Controlled Trial

This research is a follow-up study to the 3MDR study, seeking to make 3MDR therapy more widely available. The CAREN is a million-dollar environment that is only available in a small number of medical facilities worldwide. A less expensive and more feasible delivery mechanism is required to make it available to larger numbers with PTSD. The research study will randomize 60 participants with PTSD to 10-14 sessions of 3MDR delivered in the CAREN versus 3MDR delivered via the Microsoft Hololens2, an augmented reality head-mounted device, with a conventional treadmill. The primary outcome measure is the Clinician-Administered PTSD Scale (CAPS-5). As of November 2021, IRB approval has been obtained, supplies and staff are in place, and the virtual reality environment is being adapted from the CAREN to the Hololens2 to begin staff training and participant enrollment in FY22.

Morning Bright Light Therapy to Improve Sleep, Sleep-Related Outcomes, and Biomarkers in Veterans (LION)

Morning bright light therapy (MBLT) is a simple, cost-effective, home-based sleep intervention successfully used to treat sleep and behavioral disturbances and patients with neurologic/neuropsychiatric disorders (e.g., Alzheimer's dementia, schizophrenia, and Huntington's disease). Morning bright light effects are likely pleiotropic, with direct effects on sleep, circadian realignment, and mood. This research is a

randomized, blinded, placebo-controlled trial that compares a sleep intervention to a placebo device and examines the efficacy of MBLT on sleep quality and brain-based biomarkers in Veterans with mTBI.

This study aims to investigate the effects of MBLT on subjective and objective measures of sleep quality, cognition, pain, and brain-based biomarkers. Veterans with TBI will be recruited using approved advertising (e.g., internet-based, social media, radio), through data repositories, clinician referral from the Portland VA Sleep Disorders Clinic, and clinician referral from other related outpatient clinics. The trial will be conducted at the VA Portland Health Care System.

Primary outcomes will include subjective sleep metrics measured by validated questionnaires, while exploratory outcomes will consist of objective sleep metrics measured by actigraphy (e.g., relative amplitude, inter-daily stability, sleep efficiency, sleep latency) and indices of cognitive function (memory, learning, and concentration) and mental health symptoms (e.g., depression and PTSD), and quality of life/functional outcomes (e.g., pain). Biofluids, including saliva and sweat, will be collected, and assays will be performed in the laboratory. The researchers will determine if these blood-based brain biomarkers change following MBLT, are related to changes in neurobehavioral symptoms or deficits, and if any of these biomarkers predict Veterans who will be responsive to this intervention.

A Randomized, Controlled, Blinded Study of Internet-Guided Cognitive Behavioral Therapy for Insomnia in Military Service Members with Traumatic Brain Injury (eCBT-I)

Conventional in-person cognitive behavioral therapy for insomnia (CBT-I) has been proven effective in treating insomnia for the general population. However, the effectiveness of a novel form of CBT, internet-guided CBT-I (eCBT-I), has yet to be determined for Service members and Veterans with a history of TBI. Researchers at the Uniformed Services University will investigate the effectiveness of eCBT-I in treating insomnia for military Service members and Veterans with a history of TBI.

The target sample will be roughly 200 male and female Service members or Veterans between the ages of 18 and 64. Participant criteria include overt clinical insomnia for at least one month prior to informed consent by self-reported ISI (score > = 15) and PSQI (score > = 5), and history of (blast-related) TBI > = six months prior to consent, confirmed by a telephone-administered TBI screener. Eligible participants will participate in this two-year, Internet-based, virtual study by logging in to Sleep Healthy Using The internet (SHUTi) platform at their convenience via a personal computer, tablet, or smartphone. They will undergo a self-guided treatment intervention through the platform, designed to replicate an in-person therapeutic intervention for insomnia. In-person psychotherapy sessions are prohibited.

The study period consists of 60 days of eCBT-I and a three-month follow-up to assess the chronic effects of eCBT-I on insomnia. Weekly study participation varies from one to two hours depending on the pace and activities involved, such as sleep diaries and a brief sleep restriction period for active patients. After completing the three-month follow-up, all participants will be offered to partake in eCBT-I to potentially improve their insomnia symptoms by joining the education control group, which will offer open-label intervention with eCBT-I at no cost.

A Single-Blind, Randomized, Controlled Trial of a Cognitive-Behavioral Therapy Intervention Delivered by a Smartphone Application to Combat Symptoms of Depression in Service Members and Veterans with a History of Concussive Traumatic Brain Injury (ACDC)

There is a high prevalence of depressive symptoms following concussive TBI in Service members and Veterans. Still this population has cited practical reasons (e.g., privacy, time, and location) for underutilizing traditional therapy. The purpose of this study is to test the development of a self-led cognitive-behavioral therapy (CBT) mobile application to treat depression for Service members and Veterans who cannot receive treatment in person. The study aims to assess the efficacy of a novel, interactive, structured CBT digital therapeutic application for U.S. military Service members and Veterans with depressive symptoms and a history of concussive TBI.

A sample size of about 200 current and former military personnel will be randomly assigned 1:1 to either the ACDC treatment intervention group or a control group. The target population is Service members and Veterans with a wide range of depressive symptoms as indicated on the Patient Health Questionnaire – 9 and a history of concussive TBI confirmed by a TBI screener. If proven effective, this evidence-based treatment intervention will be a valid alternative, offering considerable advantages related to privacy, flexibility, and accessibility for remote patients. Results from this trial are expected to significantly benefit Service members and Veterans suffering from depressive symptoms. They may also be relevant to some civilians with similar symptoms or conditions.

Single-Blind, Randomized, Controlled Pilot Trial of a Cognitive-Behavioral Therapy Digital Therapeutic Delivered by a Smartphone Application for Posttraumatic Headaches in Military Service Members and Veterans with History of Concussive Traumatic Brain Injury (AMMO)

Prior research has revealed that 98 percent of the military population perceive having chronic posttraumatic headaches (PTH) to be related to a mild traumatic brain injury (TBI). However, only 37 percent qualify diagnostically by the International Classification of Headache Disorders for PTH within seven days of a head injury (Theeler, Flynn, & Erickson, 2010). This study is a single-blind, randomized, controlled, intervention pilot that will invent and test a digital cognitive-behavioral treatment, AMMO digital therapeutic (DTx), for PTH following a TBI.

The pilot study aims to assess the effectiveness, safety, tolerability, acceptability, and feasibility of this novel, interactive, structured cognitive-behavioral DTx for U.S. military Service members and Veterans with a history of concussive TBI. Due to the likelihood or absence of an official diagnosis, Service members and Veterans who self-report the clinical characteristics of PTH will be included in this study.

The target population is 100 Service members and Veterans with any clinical characteristics or form of PTH (e.g., migraine, cervicogenic, cluster, and tension-types). The trial will randomize these participants to either a digital intervention or a comparison control group at a 1:1 ratio. Through November 2021, the study team has obtained scientific review and approval of the research project and completed development of the therapeutic framework. The digital therapeutic program is nearing overall completion. The coaches have been established and the videos in the app have been filmed. Currently, researchers are identifying an app developer to contract with.

Photo credit: Lance Cpl. Sarah Petrock/U.S. Marine Corps

Conclusion

Warfighter blast injury continues to be a complex problem, with many sources of injury, and a dynamic threat environment. BIRCO's vision "To establish and maintain 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" highlights the need for collaborative research and knowledge sharing among DOD, non-DOD agencies, academics, and industry. This FY21 Annual Report to the Executive Agent features many innovative and technological research initiatives at the forefront of addressing the prevention, mitigation, and treatment of blast injuries and demonstrates how blast-related research gaps are being closed. Ongoing studies are working to address a greater understanding of the extent of blast exposure occurring during heavy weapons training and the potential effects on the brain; injury thresholds, dose-response relationships, or extent and duration of the physiologic and clinical impact of repeated sub-concussive blast exposure; wound infection as a major threat to life and restoration of function in casualties surviving past the first 24 hours of limb trauma; effects of single and repetitive blasts on the pharmacokinetics and pharmacodynamics of antibiotics; hazardous chemical exposure with bomb demolition, and whether it might further augment the impact of physical and psychological trauma on the brain; and the mechanisms and contributing factors associated with tinnitus onset and progression to chronic tinnitus. BIRCO continues to align its efforts to shape the evolving research landscape with a patient-centered paradigm, improving bench-to-bedside strategies to better meet Service members' needs. BIRCO will continue to strengthen the mission of the EA by driving collaboration and knowledge sharing within the blast injury research community to improve the prevention, mitigation, and treatment of our Warfighters today and into the future.

Photo credit: Senior Airman Duncan Bevan/U.S. Air Force

APPENDIX A: ACRONYMS

A

AASLT	101st Airborne Division
ABS	Advanced Blast Simulator
AC	Auditory Cortex
ACDC	Cognitive-Behavioral Therapy Intervention Delivered by a Smartphone Application to Combat Symptoms of Depression in Service members and Veterans with a History of Concussive Traumatic Brain Injury
ACH	Advanced Combat Helmet
ACTH	Adrenocorticotropic Hormone
AENC	Acute Effects of Neurotrauma Consortium
AFC	Army Futures Command
AFMES	Armed Forces Medical Examiner System
AFRICOM	United States Africa Command
AHE	Acute Hypotensive Episode
AIS	Abbreviated Injury Scale
AMG	Amygdala
AMMO	Cognitive-Behavioral Therapy Digital Therapeutic Delivered by a Smartphone Application for Post-Traumatic Headaches in Military Service members and Veterans with History of Concussive Traumatic Brain Injury
AMNS	Airborne Mine Neutralization System
ANOR	Allowable Number of Rounds
APHC	U.S. Army Public Health Center
App	Application
AR	Augmented Reality
AR	Army Regulation
ARA	Applied Research Associates, Inc.
ARL	U.S. Army Research Laboratory
AROC	Army Requirements Oversight Council
ASBREM CoI	Armed Services Biomedical Research, Evaluation, and Management Community of Interest
ASD(HA)	Assistant Secretary of Defense for Health Affairs
ATBI	Analyzer, Traumatic Brain Injury
ATC	U.S. Army Aberdeen Test Center
ATD	Anthropomorphic Test Device
AVT	Applied Vehicle Technology Panel
AWARD	Automatic Waveform Anomaly Real-Time Detector
Aβ	Amyloid Beta

B

BABT	Behind-Armor Blunt Trauma
BBB	Blood-Brain Barrier
BDNF	Brain-Derived Neurotrophic Facter
BEACH	Blast Exposure And Chemical Hazards
BECIR	Blast Exposure and Concussion Incident Report
BEMMTO	Blast Exposure Monitoring in Military Training and Operations
BESS	Blast Exposure Surveillance System
BETS	Blast Exposure Threshold Survey
BHRC	Brain Health Research Coordinator
BHSAI	Biotechnology High Performance Computing Software Applications Institute
BI/HIST	Biomedical Informatics / Health Information Systems & Technology
BIHIL	Blast-Induced Hearing Loss
BIPSR	Blast Injury Prevention Standards Recommendation
BIRCO	DOD Blast Injury Research Coordinating Office
BMJ	British Medical Journal
BOP	Blast Overpressure
BOS	Blast Overpressure Studies

BOS-D	BOS-De-Identified
BOS-L	BOS-Longitudinal
BOS-P	BOP Exposure Monitoring and Surveillance
BOS-S	BOS-Surveillance
BR	Blast-Related
BSA	Body Surface Area
bTMI	Blast-Induced Traumatic Brain Injury
BUMED	U.S. Navy Bureau of Medicine
BVF	Bone Void Fillers
BW	Blast Wave

C

C4	Composition 4
CAC	Common Access Card
CAP	Consortium to Alleviate PTSD
CAPS-5	Clinician Administered PTSD Scale
CARE	Concussion Assessment, Research, and Education
CAREN	Computer Assisted Rehabilitation Environment
CASA	CNRM's Collection, Access, Sharing, and Analytics
CAVRN	Collaborative Auditory Vestibular Research Network
CBT-I	Cognitive Behavioral Therapy for Insomnia
CC	Corpus Callosum
CCC	Combat Casualty Care
CCCRP	Combat Casualty Care Research Program
CCDC	Combat Capabilities Development Command
CCMD	Combatant Commands
CDID	Capability Development and Integration Directorate
CDMRP	Congressionally Directed Medical Research Programs
CDRT	Capabilities Development for Rapid Transition
CENC	Chronic Effects of Neurotrauma Consortium
CENTCOM	U.S. Central Command
CF	Conventional Forces
CFDRC	CFD Research Corporation
CG	Coordinating Group
CGRP	Calcitonin Gene-Related Peptide
CHeT	University of Rochester, Center for Health Technology
CHIMERA	Closed-Head Impact Model of Engineered Rotational Acceleration
CIAT	Counter-Intelligence Analytic Team
CMWG	Computational Modeling of Human Leathality, Injury, and Impairment
CNA	Capability Needs Assessment
CNRM	Center for Neuroscience and Regenerative Medicine
CoA	Course-of-Action
COA	Clinical Outcome Assessment
CoBi	Computational Biology
CoE	Centers of Excellence
CoI	Community of Interest
COIR	Current Operations Incident Report
CONUS	Continental U.S.
COTS	Commercial Off The Shelf
CPD	Capability Production Document
CPG	Clinical Practice Guideline
CRF	Case Report Form
CRM	Clinical and Rehabilitative Medicine
CRSR	USU Center for Rehabilitation Sciences Research
CSO	Collaboration Support Office
CSWBH	Comprehensive Strategy and Action Plan for Warfighter Brain Health
CT	Computerized Tomography
CTE	Chronic Traumatic Encephalopathy
CUI	Controlled Unclassified Information

D

DA PAM	Department of the Army Pamphlet
DAC	U.S. Army Combat Capability Development Command Data and Analysis Center
DARPA	Defense Advanced Research Projects Agency
dB	Decibels
DCOT	Defense Committee on Trauma
DCR	DOTmLPF-P Change Recommendation
DCR	Damage-Control Resuscitation
DE	Directed Energy
DEERS	Defense Enrollment Eligibility Reporting System
DEVCOM	U.S. Army Combat Capability Development Command
DHA	Defense Health Agency
DHP	Defense Health Program
DHS	Decompensated Hemorrhagic Shock
DMR	Differentially Methylated Regions
DMRDP	Defense Medical Research and Development Program
DNA	Deoxyribonucleic Acid
DOD	Department of Defense
DODD	DOD Directive
DODI	DOD Instruction
DOEHRS	Defense Occupational and Environmental Health Readiness System
DOEHRS-IH	Defense Occupational and Environmental Health Readiness System – Industrial Hygiene
DOT	U.S. Department of Transportation
DOTMLPF-P	Doctrine, Organization, Training, Materiel, Leadership and Education, Personnel Facilities, and Policy
DOW	Died of Wounds
DPR	Direct Peritoneal Resuscitation
DTS	Diversified Technical Systems
DTx	Digital Theraputic
DVBIC	Defense and Veterans Brain Injury Center
DVCIPM	Defense and Veterans Center for Integrative Pain Management
DVD	Dizziness or Vestibular Diagnosis
DVM	Doctor of Veterinary Medicine

E

E-CRF	Electronic Case Report Form
EA	Executive Agent
EACE	DOD/VA Extremity Trauma & Amputation Center of Excellence
EB-COP	Evidence-Based Clinical Outcome Assessment Platform
eCBT-I	Internet-guided Cognitive Behavioral Therapy for Insomnia
ECH	Enhanced Combat Helmet
EEG	Electroencephalographic
EHR	Electronic Health Records
ELISA	Enzyme-Linked Immunosorbent Assays
EMED	Expeditionary Medical Encounter Database
EOD	Explosive Ordnance Disposal
EPIC	Excellence in Prehospital Care
ERDC	Engineer Research and Development Center
ESiT	Environmental Sensors in Training
ESP	Excitatory Postsynaptic Potentials
ET	Exploratory Team
EUCOM	U.S. European Command
EV	Extracellular Vesicle
EXSUM	Executive Summary

F

FAST CT	Fast Automated Signal Transformation for Combat Training
FDA	U.S. Food and Drug Administration
FE	Finite Element
FFP	Fresh Frozen Plasma

FITBIR	Federal Interagency Traumatic Brain Injury Research
fMRI	Functional MRI
FVL	Future Vertical Lift
FY	Fiscal Year

G

GBEV	Generalized Blast Exposure Value
GCS	Glasgow Coma Scale
GEN	General
GFAP	Glial Fibrillary Acidic Proteint
GRF	Ground Reaction Forces
GROA	Gastroesophageal Resuscitative Occlusion of the Aorta
GSH	Glutathione
GSSG	Glutathione Disulfide
GUID	Global Unique Identifier

H

HA	Health Affairs
Hapln2	Hyaluronan and Proteoglycan Link Protein 2
HASC	House Armed Services Committee
Hb	Hemoglobin
HBOC	Hemoglobin-Based O2 Carrier
HCE	Hearing Center of Excellence
HD	Human Dimension
Hetastarch	Hydroxyethyl Starch
HExCAT	Homeland Explosives Consequence Assessment Tool
HFM	Human Factors and Medicine
HHA	Health Hazard Assessment
HHS	U.S. Department of Health and Human Services
HIPP	Hippocampus
HIV	Human Immunodeficiency Virus
HKIA	Hamid Karzai International Airport
HLB	High Level Blast
HMGB	High Mobility Group Box
HPA	Hypothalamic-Pituitary-Adrenal
HPC WG	Health Protection Criteria Working Group
HPD	Hearing Protection Device
HPLC-MS/MS	High-Performance Liquid Chromatography - Tandem Mass Spectrometry
HPOE	Human Performance Optimization and Enhancement
HRQOL	Health-Related Quality of Life
HRRP	Hearing Restoration Research Program
HS	Hemorrhagic Shock
HuD	Hu Antigen D
HWT	Heavy Weapons Training

I

IARV	Injury Assessment Reference Values
iBIPSR	Interactive BIPSR
ICA	Independent Component Analysis
ICHD	International Classification of Headache Disorders
ICU	Intensive Care Unit
IDE	Investigative Device Exemption
IDEO	Intrepid Dynamic Exoskeletal Orthosis
IED	Improvised Explosive Device
IEES	In-Ear Exposure Sensor
IFBIC	International Forum on Blast Injury Countermeasures
IFN	Interferon
IHPS	Integrated Head Protection System
IL	Interleukin
ILER	Individual Longitudinal Exposure Record
IMU	Inertial Measurement Unit
INDOPACOM	U.S Indo-Pacific Command
INVICTA	Investigating Training Associated Blast Pathology
IO	Intraosseous
iPSC	Induced Pluripotent Stem Cell
IPT	Integrated Product Team
IRC	Injury Risk Curve
IRI	Innovative Research Interchange
ISCTM	International Society for CNS

	Clinical Trials and Methodology
ISD	Isoelectric Spreading Depolarization
ISR	Intelligence, Surveillance, Recognizance
ISS	Injury Severity Score
IST	Information Systems Technology Panel
IV	Intravenous
IV&V	Independent Verification and Validation

J

JACS	JTAPIC Analysis and Collaboration System
JCERS	JTAPIC Concussive Event Reporting System
JCIDS	Joint Capabilities Integration and Development System
JHU-APL	Johns Hopkins University Applied Physics Laboratory
JIDO	Joint Improvised Threat Defeat Organization
JIFCO	Joint Intermediate Force Capabilities Office
JINCS	JTAPIC Information and Collaboration System
JPC	Joint Program Committee
JPC-8	Clinical and Rehabilitative Medicine Research Program
JTAPIC	Joint Trauma Analysis and Prevention of Injury in Combat
JTCG-ME	Joint Technical Coordinating Group for Munitions Effectiveness
JTS	Joint Trauma System

K

KIA	Killed in Action

L

LATBI	Laboratory Assay for TBI
LBNP	Lower Body Negative Pressure
LC-MS/MS	Liquid Chromatography - Tandem Mass Spectrometry
LCDR	Lieutenant Commander
LE AIS	Lower Extremity (LE) Abbreviated Injury Scale (AIS)
LED	Light Emitting Diode
LIMBIC	Long-Term Impact of Military-Relevant Brain Injury Consortium
LIMBIC-CENC	Long-Term Impact of Military Brain Injury Consortium - Chronic Effects of Neurotrauma Consortium
LITES	Linking Investigations in Trauma and Emergency Services
LLB	Low Level Blast
LLOP	Low Level Overpressure
LNO	Liaison Officer
LOE	Level of Effort
LOI	Lines of Inquiry
LR	Lactated Ringer's
LS	Limb Salvage
LT	Limb Trauma
LTC	Lieutenant Colonel

M

M.D.	Doctor of Medicine
M&S	Modeling and Simulation
mAb	Monoclonal Antibody
MADRS	Montgomery-Asberg Depression Rating Scale
MAP	Mean Arterial Pressure
MARSOC	U.S. Marine Forces Special Operations Command
MATLAB	Matrix Laboratory
MATV	MRAP All-Terrain Vehicle
MAUT	Multi-Attribute Utility Theory
MBLT	Morning Bright Light Therapy
MCAM	Medical Cost Avoidance Model
MCBD	Medical Chem-Bio Defense
MCCDC OAD	Marine Corps Combat Development Commany/ Operations Analysis Directorate
MCDID	Maneuver Capabilities Development Integration Directorate
MDB	Multi-Domain Battle

MDD	Major Depressive Disorder
MDO	Multi-Domain Operations
MDR	Multidrug-Resistant
METRC	Major Extremity Trauma and Rehabilitation Consortium
MGN	Medial Genuculate Nuclei
MHS	Military Health System
MHS Genesis	Genesis Medical Health System
MHSRS	Military Health System Research Symposium
MID	Military Infectious Diseases
MIDRP	Military Infectious Diseases Research Program
MIL-STD	Military Standard
MOB	Military Occupational Blast
MOC	Medical Operations Cell
MOM	Military Operational Medicine
MOMRP	Military Operational Medicine Research Program
MOS	Military Occupational Specialities
MR	Magnetic Resonance
MRD	Medical Radiological Defense
MRDC	Medical Research and Development Command
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRS	Magnetic Resonance Spectroscopy
MSD	Minimum Standoff Distance
MSISRP	Medical Simulation and Information Sciences Research Program
MSKI	Musculoskeletal Injuries
mTBI	Mild Traumatic Brain Injury
MTF	Military Treatment Facilities
MWD	Military Working Dog

N

N3WG	Neuroscience, Neurotrauma, and Neurodegeneration Working Group
NA	No Amputation
NAA	N-Acetylaspartic Acid
NACA	N-Acetylcysteine Aminde
NAD+	Nicotinamide Adenine Dinucleotide
NASA	National Aeronautics and Space Administration
NASEM	National Academies of Sciences, Engineering, and Medicine
NATO	North Atlantic Treaty Organization
NAVAIR	Naval Air Systems Command
NAVSPECWARCOM	Naval Special Warefare Command
NAWCAD	Naval Air Warfare Center Aircraft Division
NCAA	National Collegiate Athletic Association
NCBI	National Center for Biotechnology Information
NCTH	Noncompressible Torso Hemorrhage
NDAA	National Defense Authorization Act
NDAA BOS	National Defense Authorization Act Blast Overpressure Studies
NDMC	National Defense Medical College
Nefh	Neurofilament Heavy Chain
NGCV CFT	Next Generation Combat Vehicle Cross Functional Team
NGIC/CIAD	National Ground Intelligence Center, Combat Incident Analysis Division
NHRC	Naval Health Research Center
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NICoE	National Intrepid Center of Excellence
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NIPR	Non-Secure Internet Protocol Router
NMRC	Naval Medical Research Center
NMSG	NATO Modelling and Simulation Group

NOiSE	Noise Outcomes in Servicemembers Epidemiology
NORTHCOM	U.S. Northern Command
NRAP	National Research Action Plan
NRL	Naval Research Laboratory
NSC	Neural Stem Cell
NSE	Neuron-Specific Enolase
NSMRL	Naval Submarine Medical Research Laboratory

O

OASD(HA)	Office of the Assistant Secretary of Defense for Health Affairs
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OM	Operation Manager
OND	Operation New Dawn
ONR	Office of Naval Research
OPORP	Orthotics and Prosthetics Outcomes Research Program
OPR	Office of Primary Responsibility
OSA	Obstructive Sleep Apnea
OSD	Office of the Secretary of Defense
OSD(HA)	Office of the Secretary of Defense for Health Affairs
OUSD(R&E)	Office of the Under Secretary of Defense for Research and Engineering

P

PA	Pseudomonas Aeruginosa
PA	Primary Amputation
PAD	Program Area Directorates
PANTHER	Physics-Based Neutralization of Threats to Human Tissues and Organs
PAO	Public Affairs Officer
Par1	Partitioning-Defective 1
PBIED	Person Borne Improvised Explosive Device
PCA	Principal Component Analysis
PCE	Potentially Concussive Event
PCLC	Physiological Closed-Loop Control
PCR	Polymerase Chain Reaction
PDHA	Post Deployment Health Assessment
PE	Prolonged Exposure
PEDB	Physical Evidence Data Base
PEO	Program Executive Office
PET	Positron Emission Tomography
PFC	Prolonged Field Care
PFC	Prefrontal Cortex
PFE	Prosthetic Foot Emulator
Ph.D.	Doctor of Philosophy
PH/TBIRP	Psychological Health / Traumatic Brain Injury Research Program
PHCoE	Psychological Health Center of Excellence
PHI	Protected Health Information
PII	Personally Identifiable Information
PK	Pharmacokinetics
PM ICE	Program Manager Infantry Combat Equipment
PM JLTV	Program Manager Joint Light Tactical Vehicle
PM SSV	Program Manager Soldier Survivability
PMHS	Post-Mortem Human Subjects
PMO	Program Management Office
POI	Point of Injury
PolyHb	Polymerized Human Hemoglobin
PPE	Personal Protective Equipment
pRBC	Packed Red Blood Cell
pREBOA	Partial REBOA
PROMMTT	Prospective Observational Multicenter Major Trauma Transfusion
PRORP	Peer Reviewed Orthopaedic Research Program
PTH	Post-Traumatic Headache
Pto2	Partial Pressure of Oxygen

PTOA	Post-Traumatic Osteoarthritis
PTS	Post-Traumatic Stress
PTSD	Post-Traumatic Stress Disorder
PTSD-DT	PTSD Drug Treatment Program
PUFA	Polyunsaturated Fatty Acids
PVN	Paraventricular Nucleus
Pvt	Private

Q

QOL	Quality of Life
QUINT	QUantitative INstrumented Torso

R

R&D	Research and Development
RBC	Red Blood Cell
RCT	Randomized Control Trial
RDECOM	U.S. Army Research, Development and Engineering Command
RDT&E	Research, Development, Test, and Evaluation
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
RFI	Request for Information
RMTK	Range Manager Toolkit
RNA	Ribonucleic Acid
ROD/RON	Remain Over Day/Remain Over Night
ROPE	Recurrent Occupational Overpressure Exposure
RSCBE	Repeated Subconcussive Blast Exposure
rsfMRI	Resting-State fMRI
RSO	Range Safety Officer
rSO2	Regional Tissue Oxygenation
RTD	Return to Duty
RTG	Research Task Group
RTG	Research Technical Group
RTM	Reconsolidation of Traumatic Memories
rTMS	Repetitive Transcranial Magnetic Stimulation
RTR	Reconstructive Transplantation Research
RTRP	Reconstructive Transplantation Research Program

S

S&T	Science and Technology
SA	Soft-Armor Vest
SA	Secondary Amputation
SAS	Systems Analysis and Studies Panel
SASC	Senate Armed Services Committee
SBIR	Small Business Innovation Research
SCI	Systems Concepts and Integration Panel
SCI	Spinal Cord Injury
SCRIP	Spinal Cord Injury Research Program
SD	Standard Deviation
SD	Spreading Depolarization
SDH	Subdural Hematoma
SECARMY	Secretary of the Army
SECDEF	Secretary of Defense
SET	Sensors and Electronics Technology Panel
Sgt	Sergeant
SHUTi	Sleep Health Using The internet
SiMLR	Similarity-Driven Multi-View Linear Reconstruction
SIPR	Secure Internet Protocol Router
SLAD	Survivability/Lethality Analysis Directorate
SM	Service Members
SME	Subject Matter Expert
SNS	Sympathetic Nervous System
SO	Special Operators
SOCM	Special Operations Combat Medic
SOCOM	U.S. Special Operations Command
SOF	Special Operations Forces
SOHA	Service Member Occupational Health Assessment
SoS	State-of-the-Science
SOS	Smart Oxygenation System

SOT	Sensory Organization Test
SOUTHCOM	U.S. Southern Command
Spc	Specialist
SPL	Sound Pressure Level
SPS	Soldier Protection System
STO	Science and Technology Organization
STRATCOM	U.S. Strategic Command
STRONG STAR	South Texas Research Organizational Network Guiding Studies on Trauma and Resilience
STS	Significant Threshold Shifts
STTR	Small Business Technology Transfer Program

T

T&E	Test and Evaluation
TAC	Traumatic Brain Injury Advisory Committee
TATRC	Telemedicine and Advanced Technology Research Center
TB	Temporal Bone
TBI	Traumatic Brain Injury
TBI-DT IPT	Traumatic Brain Injury Drug Treatment Integrated Product Team
TBICoE	TBI Center of Excellence
TBIPHRP	Traumatic Brain Injury and Psychological Health Research Program
TBSA	Total Body Surface Area
TCD	Transcranial Doppler
TDP	TAR DNA Binding Protein
TED Initiative	TBI Endpoints Development Initiative
TFF	Total Force Fitness
TGI	Toxic Gas Inhalation
TGI	Gastrointestinal Temperature
TIDOS-IDCRP	Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study
TLR	Toll-like Receptors
TNF	Tumor Necrosis Factor
TPC	Trunk Postural Control
TRACK	Transforming Research and Clinical Knowledge
TRACK-TBI NET	Transforming Research and Clinical Knowledge for Traumatic Brain Injury Network
TRADOC	U.S. Army Training and Doctrine Command
TRANSCOM	U.S. Transporation Command
Trkb	Tropomycin-Related Kinase B
TROOPS	TBI Research Opportunities and Outreach for Participation in Studies
TSWG	Technical Support Working Group
TTMs	Technical Team Members
TTP	Tactics, Techniques, and Procedures
TXA	Tranexamic Acid

U

U.S.	United States
UARC	University-Affiliated Research Center
UBB	Underbelly Blast
UK	United Kingdom
USAARL	U.S. Army Aeromedical Research Laboratory
USAIRS	U.S. Army Institute of Surgical Research
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRDC	U.S. Army Medical Research and Development Command
USARIEM	U.S. Army Research Institute of Environmental Medicine
USASOC	U.S. Army Special Operations Command
USD	U.S. Dollars
USD R&E	Under Secretary of Defense for Research and Engineering
USMC	United States Marine Corps
USSOCOM	United States Special Operations Command

USU	Uniformed Services University of the Health Sciences
USUHS	Uniformed Services University of the Health Sciences

V

VA	U.S. Department of Veterans Affairs
VAID	Visual Anatomical Injury Descriptor
VAMC	VA Medical Center
VBA	Veteran's Benefit Administration
VCA	Vascularized Composite Allotransplantation
VML	Volumetric Muscle Loss
VOMS	Vestibular and Oculomotor Systems
VPS	Vehicle Protection Suite
VR	Virtual Reality

W

WBH	Warfighter Brain Health
WIA	Wounded In Action
WIAMan	Warrior Injury Assessment Manikin
WPAC	Warfighter Protection and Acute Care
woSA	Without Soft-Armor
WRAIR	Walter Reed Army Institute of Research
WRIISC	War Related Illness and Injury Study Center
WRNMMC	Walter Reed National Military Medical Center
WW	Wounded Warrior

Y

YFP	Yellow Fluorescent Protein

OTHER

2 BCT	2nd Brigade Combat Team
3D	Three Dimensional
3MDR	Motion-assisted, Multi-modular Memory Desensitization and Reconsolidation

Photo credit: Taylor Curry/U.S. Navy

Photo credit: Cpl. Scott Jenkins/U.S. Marine Corps

APPENDIX B:

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APPENDIX C:

DODD 6025.21E

Department of Defense

DIRECTIVE

NUMBER 6025.21E
July 5, 2006
Incorporating Change 1, October 15, 2018

USD(R&E)

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"[1]
(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).

1 Federal legislative information is available through the Library of Congress THOMAS site, http://thomas.loc.gov.

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.

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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[2] 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, U.S. 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.

[2] CJCSI 3170.01E, "Joint Capabilities Integration and Development System," May 11, 2005, is available at http://www.dtic.mil/cjcs_directives/cjcs/instructions.htm.

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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.

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. SUMMARY OF CHANGE 1. This change reassigns the office of primary responsibility for this directive to the Under Secretary of Defense for Research and Engineering in accordance with the July 13, 2018 Deputy Secretary of Defense Memorandum (Reference (h)).

8. EFFECTIVE DATE

This Directive is effective immediately.

Gordon England

Enclosures – 3

E1. References, continued

E2. Taxonomy of Injuries from Explosive Devices

E3. ASBREM Committee

Change 1, 10/15/2018

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
(h) Deputy Secretary of Defense Memorandum, "Establishment of the Office of the Under Secretary of Defense for Research and Engineering and the Office of the Under Secretary of Defense for Acquisition and Sustainment," July 13, 2018

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.

E3. ENCLOSURE 3

ASBREM COMMITTEE

E3.1. ORGANIZATION AND MANAGEMENT

The ASBREM Committee shall:

E3.1.1. Consist of general and flag officer and Senior Executive representatives of relevant DoD Components.

E3.1.1.1. Standing members include relevant senior officials of the DoD Components. At a minimum, the DDR&E, the ASD(HA), and representatives of the DoD Components' Acquisition Executives.

E3.1.1.2. The standing membership may be expanded by invitation of the Chair when issues require senior-level coordination outside the scope of the principal members. Such invited members will include a medical flag officer from the Joint Staff, a designee of the DoD EA specified by this Directive, the Director, JIEDDO, the Director of the Combating Terrorism Technology Support Office, and others as appropriate.

E3.1.2. Be chaired by the DDR&E or Senior Executive designee and co-chaired by the ASD(HA) or Senior Executive designee.

E3.1.3. Convene at the discretion of the Chair and Co-chair.

E3.1.4. Invite the attendance of observers from DoD boards, committees or offices, or from other Federal Agencies with interests in the deliberations of the ASBREM Committee.

E3.1.5. Establish subcommittees, Joint Technology Coordinating Groups, and other entities, as required, to facilitate and execute committee business.

E3.2. FUNCTIONS

The ASBREM Committee shall:

E3.2.1. Review medical RDT&E program plans and accomplishments for quality, relevance, and responsiveness to military operational needs, the needs of the Military Health System, and the goals of Force Health Protection.

E3.2.2. Review program plans and budgets in support of the various guidance documents relevant to National Security and to the missions and functions of the Department of Defense.

E3.2.3. Provide coordination, recommendations, and support to DoD EA(s) and other DoD officials as requested, directed, or otherwise appropriate.

Photo credit: Staff Sergeant Liliana Moreno/U.S. Air Force

Photo credit: Sgt. Sarah Sangster/U.S. Army

APPENDIX D:

SUPPLEMENTAL TABLES

The Congressionally Directed Medical Research Programs (CDMRP) is a global funding organization that manages biomedical programs in cancer research, military medical research, and other disease- and injury-specific research areas. The following table lists the CDMRP research programs with recent blast injury-related research activities. More information on the CDMRP can be found at https://cdmrp.health.mil.

CDMRP Research Program	Program Focus
Chronic Pain Management Research Program (CPMRP)	The **CPMRP** funds research efforts focused on the prevention and improved management of chronic pain in Service members, Veterans, and the American public. CPMRP places specific emphasis on the utilization of non-opioid interventions to combat persistent and recurrent pain. Example focus areas relevant to blast injury: • Chronification of pain (i.e., the transition of acute pain to chronic pain) • Development of novel non-opioid therapies and methods for treatment of chronic pain • Implementation Science and Comparative Effectiveness (for evidence-based, efficacious interventions to manage or prevent chronic pain) • Observational studies related to chronic pain (i.e., relationships between comorbidities and pain)
Combat Readiness Medical Research Program (CRRP)	The **CRRP** funds research relating to the development of military-relevant advanced technology and therapeutic research focused on forward-deployable solutions that can promptly address life threatening injuries, medical threats, and treatments for Warfighters in battlefield settings. Example focus areas relevant to blast injury: • Multiple-use scalable wound care solutions • Repair and/or restoration of combat-related genitourinary organ and tissue damage • Solutions for the assessment of mild traumatic brain injury (mTBI) in deployed and far-forward settings, to include portable devices • Freeze-dried plasma and platelets for hemorrhage control and resuscitation • Enhanced delivery and utilization of telemedicine platforms
Epilepsy Research Program (ERP)	The **ERP** funds research to develop an understanding of the magnitude of post-traumatic epilepsy (PTE) within the military and to expand research into the basic mechanisms by which TBI produces epilepsy. Example focus areas relevant to blast injury: • Markers and Mechanisms: Identifying biomarkers or mechanisms of PTE • Epidemiology: Epidemiological characterization of PTE following TBI • Longitudinal Studies: Studies of the evolution of PTE • Innovative Research: Tools intended to better inform or improve upon PTE research and care

CDMRP Research Program	Program Focus
Hearing Restoration Research Program (HRRP)	The **HRRP** funds innovative research that has the potential to maximize operational performance, medical readiness, and quality of life for Service members, Veterans, and others living with significant auditory system injuries. Example focus areas relevant to blast injury: • Accelerate the translation of biological regeneration/repair mechanisms into therapies that treat auditory system injury and restore auditory function • Diagnostic tests that help differentiate sensory, neural, synaptic, and central processing disorders, that may inform applicability and outcomes for current or future hearing restoration therapeutics • Develop reliable in vitro human models to facilitate the understanding, derivation, and characterization of human auditory cells, and/or to facilitate the evaluation of hearing restoration therapies • Develop and/or validate techniques/methods beyond the audiogram to diagnose acute auditory system injury in austere or remote environments
Joint Warfighter Medical Research Program (JWMRP)	The **JWMRP** funds the logical continuation of mature research projects close to yielding tangible benefits to military medicine across five research areas: Medical Simulation and Information Sciences, Military Infectious Diseases, Military Operational Medicine, Combat Casualty Care, and Radiation Health Effects. Input into Joint and Service-specific medical requirements and capability gaps is obtained through coordination with the Defense Health Agency, Army, Navy, and Air Force. Example projects relevant to blast injury: • Use of virtual technology to improve cognitive and functional deficits in individuals with traumatic brain injury • Development of an ultra-wideband wearable ultrasound probe for battlefield use • Development of a thermoresponsive reversible adhesive for temporary intervention of ocular trauma • Use of light-activated sealing to improve outcomes following penetrating bowel trauma • Development of a non-invasive, compact portable monitor to assess intracranial pressure • Use of autologous bone marrow mononuclear cells to treat adult severe traumatic brain injury • Development of an implantable pudendal nerve stimulator to restore bladder function in humans after spinal cord injury • Development of a moisture management liner and active cooling system for lower limb prostheses to improve fit, comfort, and residual limb skin care

CDMRP Research Program	Program Focus
Military Burn Research Program (MBRP)	The **MBRP** 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. Example focus areas relevant to blast injury: • Development of interventions or therapies that can help, accelerate, or optimize wound healing • Development or refinement of interventions or technologies that will enable non-burn specialists, such as a field medic/ corpsman/paramedic, to provide good burn care closer to the point of injury allowing for better long-term outcomes • Development of therapeutic interventions that can help treat debilitating scars and prevent contractures • Advancement of standard of care practices through the conduct of high impact clinical trials
Neurotoxin Exposure Treatment Parkinson's (NETP) *Note: This program will be split into two programs for FY22. The neurotoxin exposure research will be rolled into the Toxic Exposures Research Program and the Parkinson's research will be in the Parkinson's Research Program.*	The **NETP** program supports Parkinson's disease (PD) research, investigating the underlying biologic mechanisms of and therapeutic interventions for the neuro-degenerative effects of deployment, environmental, and occupational exposures in Service members and Veterans. Example focus area relevant to blast injury: • Quantifiable gene–environment interactions and the risk for or progression of Parkinson's disease following neurotoxin exposure • How traumatic brain injury (TBI) influences the risk for PD
Orthotics and Prosthetics Outcomes Research Program (OPORP)	The **OPORP** funds research that evaluates orthoses and/or prostheses using patient-centric outcomes relevant to Service members, Veterans, and other individuals with limb loss and/or limb impairment. The intent of this research is to generate clinically useful evidence that will enhance and optimize patient outcomes. Example focus areas relevant to blast injury: • Orthoses or Prostheses Form – Optimize patient outcomes through the analysis and characterization of variables related to the form of currently available clinical options, such as device size, shape, material, and/or configurations • Orthoses or Prostheses Fit – Optimize patient outcomes related to human-device interface through the analysis of variables in currently available clinical options that facilitate fit-related metrics such as comfort and/or usability • Orthoses or Prostheses Function – Optimize patient outcomes through the analysis of variables related to currently available device function, such as device control, sensors, and passive or active response, with respect to activities of daily living and other real-world activities

CDMRP Research Program	Program Focus
Peer Reviewed Alzheimer's Research Program (PRARP)	The **PRARP** funds research that addresses the long-term consequences of TBI as it pertains to Alzheimer's disease (AD) and Alzheimer's disease related dementias (ADRD). Example overarching challenges relevant to blast injury: • Foundational Research: Research to examine the interrelationship between traumatic brain injury, military service-related factors, and subsequent AD/ADRD • Diagnostics, Prognostics and Environmental factors: The need for technologies, tests, questionnaires, devices, biomarkers, or analyses to detect the relationship between military service-related risk factors and AD/ADRD, including epidemiological research to examine the interrelationship between military service, risk and resiliency factors, and subsequent AD/ADRD
Peer Reviewed Medical Research Program (PRMRP)	The **PRMRP** funds research across the full range of science and medicine, with an underlying goal of enhancing the health, care, and well-being of military Service Members, Veterans, retirees, and their family members. Example focus areas relevant to blast injury: • Hemorrhage Control • Hydrocephalus • Non-Opioid Therapy for Pain Management • Pathogen-Inactivated Blood Products • Peripheral Neuropathy • Sleep Disorders & Restriction
Peer Reviewed Orthopaedic Research Program (PRORP)	The **PRORP** 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. Example focus areas relevant to blast injury: • Diagnostic and treatment strategies for compartment syndrome • Development of rapid limb stabilization and novel wound protectants for severely wounded limbs to enable transport • Development and optimization of battlefield-feasible diagnostic capabilities, decision support tools, interventions, and rehabilitation strategies that can facilitate retention on duty • Development of advanced tissue regeneration therapeutics in nerve, muscle, and/or composite tissue for the restoration of traumatically injured extremities • Identification of best practices to address infection at the skin-implant interface for osseointegrated prosthetic limbs

CDMRP Research Program	Program Focus
Reconstructive Transplant Research (RTR) Program	The **RTR Program** 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. Example focus areas relevant to blast injury: • Reduce the risks of VCA-associated immunosuppression • Develop reliable non-invasive prognostic/diagnostic biomarkers, methods, or tools for monitoring VCA graft rejection, including applications that would be suitable for point-of-care testing or home monitoring
Spinal Cord Injury Research Program (SCIRP)	The **SCIRP** funds collaborative research to advance the treatment and management of spinal cord injury (SCI) and ameliorate its consequences relevant to injured Service members. Example focus areas relevant to blast injury: • Identifying and validating biomarkers for diagnosis, prognosis, and for evaluation of treatment efficacies • Preserving and protecting spinal cord tissue at time of injury for improved neurologic outcomes • Rehabilitation and regeneration – maximizing the function of the residual neural circuitry, including harnessing neuroplasticity and recovery to improve function after SCI • Psychosocial issues relevant to people with SCI, their families, and/or their care partners
Toxic Exposures Research Program (TERP)	The Consolidated Appropriations Act, 2022 established the **TERP** as a new broader program directed to support research related to four major areas that were translated into the 4 Topic Areas for the FY22 TERP. These Topic Areas may be relevant to blast injury if there is a toxic exposure following a blast however, blast injury is not the primary focus of the TERP. The FY22 TERP Topic Areas include: • Neurotoxin Exposure • Gulf War Illness and Its Treatment • Airborne Hazards and Burn Pits • Other Military Service-Related Toxic Exposures in General, Including Prophylactic Medications, Pesticides, Organophosphates, Toxic Industrial Chemicals, Materials, Metals and Minerals

CDMRP Research Program	Program Focus
Traumatic Brain Injury and Psychological Health (TBIPHRP)	The **TBIPHRP** funds research efforts aimed at improving prevention, detection, and treatment of TBI and psychological health disorders. Research funded by TBIPHRP spans the translational research spectrum from basic research to clinical trials. Example focus areas relevant to blast injury: • Computational models from clinical data to forecast the long-term and/or late effects of brain exposures, such as TBI, and co-occurring conditions • Identification and validation of biomarkers or other objective markers for diagnosis, prognosis, or monitoring of TBI • Interventions focused on sensory and motor dysfunction after brain injury • Interventions that address neurodegenerative processes associated with TBI • Interventions that restore cognitive reserve and functioning • Translation of environmental sensor outputs to conditions within the brain • Development of innovative materials and technologies that can prevent or reduce the risk of TBI • Validation of objective tools/methods for assessing and real-time health status monitoring of TBI
Vision Research Program (VRP)	The **VRP** funds innovative research that will significantly advance the understanding, prevention, diagnosis, mitigation, and/or treatment of eye injury or visual dysfunction associated with military exposure.. Example focus areas relevant to blast injury: • Eye injury or visual dysfunction as related to military exposure • Diagnosis, stabilization, and treatment of eye injuries in austere environments and prolonged field care settings • Restoration of visual function after military exposure-related vision loss or severe visual impairment

DOD BLAST INJURY RESEARCH COORDINATING OFFICE

ADVANCING BLAST INJURY RESEARCH TO PROTECT AND HEAL THOSE WHO SERVE

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